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DISEASES OF THE BLOOD AND ATLAS OF HEMATOLOGY

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The Third Blackader Lecture

ON

RHEUMATIC FEVER AND HEART DISEASE IN CHILDREN*

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MAY I be permitted to tender my sincere thanks to this Association for the honour they have conferred on me by the invitation to deliver this address. My appreciation is the deeper since the occasion is associated with the name of my old physician, teacher and friend, Dr. A. D. Blackader. It was my good fortune all my life to be associated with Dr. Blackader. As a general practitioner he attended me in childhood, as he did most of the children of Montreal at that time; as college professor he taught me as a student; later he was associated with me on the Boards of various hospitals and institutions; and finally instructed me again when he was editor of the *Journal* of this Medical Association. Dr. Blackader was a many-sided man. He was the pioneer pædiatrist of this country, a recognized authority on materia medica and therapeutics; as administrator he was responsible for the development of many of Montreal's hospitals and charitable institutions; and as editor of the *Journal* had much to do with the establishment of this Society in its present firm and honoured position. Throughout the many activities of his long and useful life the guiding principle seems to have been his profound interest in the promotion of child-welfare in the Dominion. Therefore, in considering a subject for an address given in his memory, it seemed fitting that one should be chosen which was appropriate to the purpose to which Dr. Blackader devoted his life. Hence I have come naturally to the subject of acute rheumatism

and cardiac disease in childhood as the one which has now come to take the first place as a threatened danger to normal childhood and adolescence in this country.

It may be thought that this is an over-statement of the importance of rheumatic heart disease in America, but let me quote the opinion of some who are in a position to judge. Heart disease is the most important cause of death now registered, accounting for 10 per cent of all deaths, and exceeding all other causes of death and disease, including tuberculosis. According to the Metropolitan Life Insurance statistics a child of 10 years of age is three times as likely to die of heart disease eventually as of any other disease. In all careful routine examinations of school children in temperate climates, from 2 to 5 per cent show evidence of organic heart disease, nearly 90 per cent of which is due to rheumatic fever. The Health Department of Montreal recently stated that about 3,000 of the children attending school in Montreal showed signs of organic heart disease. This would give us a rough estimate of about 25,000 school children in Canada afflicted with rheumatic cardiac disease. Can any other serious disabling disease show such a record?

Formerly, various acute infectious diseases took first place as causes of early death, and successively typhoid fever, summer diarrhoea, and diphtheria have held this dishonourable position, but, with the steady progress of medical science and modern hygiene, these are rapidly disappearing; hence the growing importance of acute rheumatism and heart disease.

* Delivered at the Sixty-eighth Annual Meeting of the Canadian Medical Association, Ottawa, June 25, 1937.

A very few years ago tuberculosis was the outstanding threat among the chronic infections, but with the mortality from tuberculosis fallen to one-third of what it was a generation ago, the relative importance of rheumatic fever is correspondingly increased. As I said a few moments ago, rheumatic heart disease is now the outstanding threat against child health, the one serious disease of childhood which is uncontrolled, and, unfortunately, the disease about which we are most ignorant. I repeat, rheumatic fever is the most serious danger, both immediate and remote, to child life in Canada at the school ages of 5 to 14 years.

What possibilities are there of influencing the prevalence of rheumatic fever in Canada? In order to influence, let alone control, any disease, the first essential is an accurate knowledge of its predisposing and exciting causes. From the vast amount of published clinical experience and endless compiled statistics of facts about rheumatic fever in childhood we gather the following rather meagre data.

First, girls are more affected than boys, in about the proportion of 3 to 2, possibly due to a slightly different mode of life, but this factor seems of little assistance to us.

Heredity plays a part in the incidence of the disease, and there is at least a family predisposition towards rheumatism, but so far eugenics has not advanced to a degree where we can use it to influence the disease, and the only advantage of this fact seems the importance of greater care in the supervision and treatment of certain families.

Age is an important factor. All statistics show the peak of onset at 7 years of age, with an increasing tendency to serious cardiac involvement, the younger the age of onset. Hence the importance of endeavouring to protect the younger children.

Climate and latitude invariably affect the occurrence of rheumatic fever, and the frequency of the disease steadily diminishes toward the south. The disease is commoner, the nearer the coasts, and in districts with higher humidity. We cannot change our latitude or our climate, but occasionally these facts might influence the choice of residence of predisposed families with children of the more threatened ages and sex.

Respiratory and particularly throat infections have an undoubted influence on the onset of rheumatic fever and the occurrence of relapses,

and the modern care of the hygiene of the throat and removal of sources of infection may have some slight effect.

Lastly, social conditions have a vast influence on the prevalence of rheumatic fever. The disease is commoner in crowded urban districts, and much more prevalent among the poorer classes and those subjected to over-crowding, poor nutrition, and defective hygiene. It is claimed that only one case of rheumatic fever occurred in Eton Boys' School in seventeen years, yet in the public schools of the crowded districts of London at the same time nearly 5 per cent of the children had rheumatic hearts. This is surely matter for serious thought as to the possibility of affecting the incidence of the disease through the improvement of social conditions.

Coming next to the exciting cause of the disease, without a knowledge of which we cannot hope for effective effort at prevention, we may as well admit at once that we are in complete ignorance. All authorities agree that it is an infection, running a chronic course with a tendency to exacerbations, but frankly that is as far as we can go. A few years ago most investigators thought it was due to certain types or strains of the hæmolytic streptococcus, but recent studies all discourage this idea, and most take refuge in the unsatisfactory conclusion that it is probably a virus disease, with the streptococcus as a predisposing agent or secondary invader. That streptococcus infections excite its onset or provoke recurrences is obvious and unquestionable, but this is not proof that they cause the disease.

Coupled with our ignorance of the cause is the unfortunate absence of a reliable diagnostic test for the presence of the disease. No real progress was made in the struggle with tuberculosis or syphilis until we had the tuberculin reaction and the Wassermann reaction, respectively, to assist in recognizing the diseases, and so far we have no skin test, blood test or bacteriological test of any value in recognizing rheumatic infection.

Our ideas of its pathology are vague, as it shows only the proliferative lesions of chronic inflammation, and we anxiously await further light along this line. The only real advance made recently is the demonstration that it is one of the most widespread of diseases in the tissues of the body, affecting not only the heart

as a whole but practically all tissues. There are definite signs of invasion in the blood vessels, serous membranes, lungs, nervous system, skin, and, most of all, in the connective tissues all over the body, so that even syphilis and tuberculosis are scarcely so widespread and diffuse in their lesions.

The course of the disease is most variable. There is no reason for me to refer to it in detail, since we all are familiar with its various manifestations. I merely wish to emphasize that it is the most protean of all diseases, and, whether it causes arthritis, chorea, carditis or skin eruptions, it is impossible to be absolutely certain of the diagnosis in the absence of any recognized scientific test. I also wish to emphasize that the cases according to their course fall into three groups which are numerically about equal in size. The first group includes those cases progressing steadily to serious cardiac damage and inevitable death in a few weeks to a few months. The second group are those harbouring the infection for many years, with periodic exacerbations or relapses, gradually leading to complete disability and death at an early age. The third group consists of those in whom the infection dies out entirely, leaving the patient either unhurt or with cardiac lesions compatible with an active life. Roughly these groups are equal in size, and the earlier in life the disease starts, the more cases fall into the first and second groups. The whole of our endeavour at prevention and treatment is to diminish the frequency of the cases in the first and second groups and bring as many as possible into the last.

Before reviewing how we hope to accomplish this aim, let me emphasize once more the economic importance of the disease, not only in its immense mortality but in the extent of the disability it causes, the huge expense of the prolonged treatment of such a chronic infection, and the financial loss to the nation, not only from the loss of life but from the number of disabled victims who must be maintained.

Next for a few disheartened words as to our feeble efforts at the treatment of an unknown infection, which we are unable to positively recognize in a considerable percentage of cases. Specific drugs or sera we have none. The salicyl compounds relieve certain symptoms such as fever and painful arthritis, but do not cure. Even the most modern cure-all, sulphanilamide, seems entirely ineffective, possibly another argu-

ment against the streptococcus theory of causation. Rest is the most potent of all remedies, but must be carefully controlled over long periods lest it be overdone. Various forms of physiotherapy assist in the relief of symptoms.

In the Children's Memorial Hospital at Montreal, three years ago, becoming discouraged with the poor results we were securing with our ward treatment of these cases, we decided to establish a separate pavilion for the observation and treatment of cases of rheumatic cardiac disease alone, hoping that special study of the cases, special routine in the pavilion, and intensively supervised treatment would secure better results than we had obtained so far. The pavilion was constructed on the same principles as those for the treatment of tuberculosis, as we considered the principles of the management of the two classes of chronic infection were the same. It is too soon in the experiment to draw definite conclusions, but so far the entire staff of the hospital are convinced that our results are measurably improved. In particular, by close supervision of the temperature, pulse rate, body weight, blood analysis, and rate of sedimentation of the corpuscles, we can arrive at a much more accurate knowledge of the state of activity of the infection, and consequently are guided in granting permission for increased activities and exercise. The close observation of this little group of cases has only emphasized our realization of the need for prolonged treatment and more extended supervision.

Finally, if I have not entirely discouraged you by my reiterated confessions of the ignorance and impotence of the medical profession in reference to rheumatic fever, let me briefly summarize the lines along which health authorities of most countries are working in the endeavour to control the incidence of the disease.

For the control of any disease the first essential is the need of organized, cooperative effort and this is directed along the following lines. First, that provision should be made for the recognition, supervision, and after-care of cases of rheumatic fever. Time does not seem ripe for the compulsory notification of the disease, but at least some effort might be made to ascertain more accurately its extent and so enable us to assist the sufferers. Secondly, that an organized effort be made in each community to improve social conditions, particularly as regards general hygiene, housing conditions and social

conditions generally, so that the burden of the disease should not fall on one class of the community. If it is chiefly the poorer class in the congested centres which is involved can we not by improving social conditions among this class assist in stamping out the disease? Thirdly, realizing that the onset and relapses of rheumatic fever follow regularly on respiratory and throat infections, can we by intelligent directed effort lessen these infections and improve the mouth and throat hygiene of the community. Lastly, and what seems to me most important, surely in all the important centres of population and medical teaching, special facilities should be provided for the intensive study of the disease, facilities for research as to its cause and possible control, and organized effort to assist those stricken and disabled by the disease.

Let me close by a quotation from a well-known authority, giving at least a ray of encouragement, "In its typical clinical form, rheumatic fever has declined in most countries to a remarkable extent, and thus it comes within the category of those diseases of the cause of whose decrease we have no exact or complete knowledge."

No one is more conscious than myself of the vague and inconclusive account of the disease I have presented and the possible methods of its control. However, if I have done anything to call attention to this serious problem and arouse interest in it I will feel my time has been well spent, and that I have made a slight effort to follow in the footsteps of my revered teacher, Dr. Blackader.

VAGUS STIMULATION AND THE PRODUCTION OF MYOCARDIAL DAMAGE

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IN the experiments reported by Hall, Ettinger and Banting¹ it was shown that myocardial and coronary artery damage resulted from long-continued daily administration of acetylcholine to unanæsthetized dogs. Unsuccessful attempts to reproduce these conditions in other dogs by similar injections of choline (Ettinger and Hall²), by histamine (Ettinger, Hall and Lang³), by the administration of sodium nitrite, by strenuous daily exercise, and by flooding the system with low-grade infection have led us to consider the apparent specificity of acetylcholine in the production of such lesions.

Since the effects of vagus nerve stimulation are due to the action of liberated acetylcholine (Loewi and associates^{4,5,6}) then, if our supposition is correct, long-continued stimulation of the vagus nerve through liberated acetylcholine should likewise produce myocardial and coronary artery damage. Experiments of this type have been reported by Ettinger, Hall and Banting.⁷ They used two methods of stimulation: (a) stimulation from an insulated secondary coil, the electrodes of which were in contact with the exposed vagus nerve; implantation of the whole coil in the neck (a modification of the method of Loucks,

1933); (b) stimulation by means of shielded electrodes (a modification of Cannon's method, 1933), which were fastened to the vagus nerve in the neck and allowed to protrude through a stab wound in the skin. The stimulations were carried out with the animals under dial or nembutal anæsthesia. Under the conditions of these experiments, Ettinger, Hall and Banting were unable to produce degenerative changes in the heart or its blood-vessels by means of prolonged daily electrical excitation of the vagus nerve. It was thought that under more normal conditions, without deep anæsthesia, prolonged stimulation of the vagus nerve in the dog might still result in cardiac dysfunction. The following groups of experiments were therefore carried out: A. stimulation under light anæsthesia; B. stimulation without anæsthesia.

A. THE EFFECT OF CONTINUOUS STIMULATION OF THE VAGUS NERVE IN THE LIGHTLY ANÆSTHETIZED DOG

Under light nembutal anæsthesia (25 mg. per kilo) the left vagus nerve was separated from the aortic depressor nerve and cervical sympathetic. The electrode-foot was sewn around

the nerve, the lead-in wires brought to the surface, and stimulation carried out continuously in the manner already described. (Ettinger, Hall and Banting, 1936). The left vagus nerve was stimulated in each case.

One animal was given atropine throughout the stimulation period. This was found to be effective in preventing the physiological response of vagal stimulation. At the same time it does not prevent the liberation of acetylcholine following such stimulation. (Loewi and Navratil⁴). In order to accentuate the effects of vagal stimulation another animal was given eserine. This substance decreases the rate of hydrolysis of acetylcholine by inhibiting the activity of the choline-esterase. To supply nourishment and fluid to these animals normal saline and 10 per cent glucose were given occasionally (column 8, Table I).

(22 seconds between stimulating periods) the heart-rate varied from 180 to 220 beats per minute (acceleration due to anaesthesia). During stimulation this was decreased to 60 to 100 beats per minute. Towards the termination of the experiments the heart-rates were difficult to determine owing to respiratory disturbances and weakness of the heart-beat.

Gastro-intestinal.—1. Salivation occurred in all of the animals except the one receiving atropine. The animal receiving eserine secreted very large quantities of frothy saliva.

2. Vomiting occurred frequently, except in the animal receiving atropine. The vomitus at first contained some undigested food, but in the later stages was "coffee-ground" in type (positive benzidine test for presence of blood).

3. Diarrhoea and melæna were common (except in D 73 which received atropine).

TABLE I.
CONTINUOUS STIMULATION EXPERIMENTS—ANÆSTHETIZED ANIMALS

1	2	3	4	5	6	7	8
Dog No.	Total experimental time	Total stimulating time	Total off time	Total mg. atropine	Total mg. eserine	Total mg. nembital	Glucose or normal saline intravenously
D 63	31 hrs.	24½ hrs.	6½ hrs.	0	0	315 mg.	350 c.c. n.s. 300 c.c. 10% gl. 650 c.c.
D 64	36 hrs.	26 hrs.	7 hrs.	0	0	585 mg.	400 c.c. n.s. 400 c.c. 10% gl. 800 c.c.
D 71	33 hrs.	26 hrs.	7 hrs.	0	0	337.5 mg.	300 c.c. n.s. 350 c.c. 10% gl. 650 c.c.
D 72	46 hrs.	36¼ hrs.	9¾ hrs.	0	0	300 mg.	1500 c.c. 10% gl.
D 66	45 hrs.	35½ hrs.	9½ hrs.	0	62.5 mg.	435 mg.	1400 c.c. 10% gl.
D 73	70 hrs.	54½ hrs.	14½ hrs.	51.0 mg.	0	930 mg.	3500 c.c. 10% gl.

The animals were stimulated for 31 to 70 hours (column 3, Table I). Throughout the stimulation small amounts of nembital were given to maintain light anaesthesia. Heated operating tables were used to keep the animals warm.

Heart-rate.—Inhibition of the heart-rate was taken as evidence of vagal stimulation. During the early hours of stimulation this inhibition was easily detected. When not being stimulated

Autopsy.—The animals were autopsied immediately after death. With the exception of the left auricle the heart was usually filled with blood clot, which suggested complete ventricular fibrillation as the cause of death. Except for a rather large infarcted area at the base of the anterior papillary muscle in the animal which had received eserine, no gross lesions were observed in the heart. The lungs showed some areas of congestion but were otherwise normal.

Numerous hæmorrhagic areas were found throughout the gastro-intestinal tract. In one animal, D 63, which had received eserine, marked ulceration was observed in the pyloric region along the lesser curvature. General congestion of the gastro-intestinal tract was observed except in the animal which had received atropine (D 73). The intestine of D 73 appeared fairly normal, with evidence of slight congestion in the duodenum.

Microscopic examination.—Microscopic examination revealed capillary congestion and hæmorrhage in the heart with the occurrence of some early hyaline degeneration of the cardiac muscle.

The spleen contained large deposits of hæmosiderin. The lungs appeared normal, with no evidence of pneumonia. Capillary congestion was found in some of the kidney sections. All other sections taken from these animals appeared fairly normal.

Summary.—Although these experiments were carried out under light anaesthesia, they differ from those reported by Ettinger, Hall and Banting⁷ in that continuous stimulation, rather than daily prolonged stimulation of the vagus nerve, was carried out.

Microscopic examination has shown that myocardial damage has been initiated by such stimulation.

B. THE EFFECT OF CONTINUOUS STIMULATION OF THE VAGUS NERVE IN THE UNANÆSTHETIZED DOG

In order that the animals could be stimulated continuously, without anaesthesia and with perfect freedom to move about the cage, a new type slip-ring-contact described by Manning and Hall⁸ was used.

The stimulation experiments were divided into two groups. Animals in the first group received vagus stimulation, and, in addition, one animal received atropine (0.2 mg. per kilo) every hour throughout the period of stimulation. This amount was found to be effective in preventing the physiological response of vagal stimulation. Those animals in the second group received eserine (0.05 mg. per kilo per ½ hour—see discussion) in addition to vagus stimulation. All animals were fed daily, during which time the stimulation was stopped for 45 minutes every 24 hours. Water was available at all times. As the effects of the stimulation became

more marked and anorexia was evident, intravenous glucose and saline injections were given.

The animals were placed in the cages two days previous to stimulation, during which time normal electrocardiographs and resting heart-rates were taken. Fairly complete blood analyses were carried out.

Since these experiments were carried out in the unanæsthetized animal, the homolateral recurrent laryngeal nerve was cut. Changes in heart-rate and respiration were taken as the index of effective vagus stimulation. The current was altered by changing the position of the secondary coil in relation to its primary. Eleven dogs were used in these experiments.

Considerable respiratory disturbance and vomiting occurred in the early part of the stimulation. However, by altering the primary in relation to the secondary coil of the inductorium a stimulating current of sufficient strength to produce cardiac slowing without excess respiratory disturbance and vomiting was obtained.

GROUP I

Vagus stimulation.—During the first hours of stimulation the heart-rate was about normal between stimulating periods (*i.e.*, during the 22 seconds the stimulation was off). During stimulation a decrease of 20 to 30 beats per minute was detected. In some cases the resting heart-rates increased during the progress of the experiments and the degree of inhibition during stimulating periods became greater. The total stimulation time for animals in this group ranged from 70 to 93 hours and in two cases 120 hours.

Atropine produced a cardiac acceleration (160 beats per minute) which was not influenced by vagus stimulation for 160 hours.

Diarrhoea and vomiting were frequently observed, except in the animal which received atropine. The vomitus at first contained much bile-stained mucus and later coffee-ground material. These effects were first observed during the second day and are not to be confused with the preliminary distress which was corrected at the beginning of stimulation. Bouts of dyspnoea and whining occurred which became more pronounced during the latter part of the stimulation experiment. One animal in particular appeared to experience typical attacks of cardiac embarrassment evidenced by marked respiratory

distress, restlessness, whining, etc. Although murmurs were not a constant finding, systolic murmurs were detected many times throughout the experiments.

Exophthalmos of the left eye, which became more pronounced as the experiment progressed, was observed in all the animals. In many cases the nictitating membrane was completely paralyzed.

Electrocardiograph.—Changes in the shape and form of the T-wave were a very constant finding in the electrocardiograph records of these animals. In most cases the normal record showed a negative T II, which later became positive. Some records showed many reversions from negative to positive to diphasic forms. A typical example of these changes is illustrated in the following. In D 81 the normal T II was negative. After 29 hours of stimulation the resting heart-rates became faster and T II reversed. Occasional ventricular extrasystoles occurred at this time. At 58 hours the resting heart-rate had become much faster, with the re-appearance of negative T II.

Autopsy report.—On autopsy the animals appeared to be well nourished. The lungs were fairly normal with no evidence of pneumonia. The gastro-intestinal tract appeared congested with some evidence of intestinal bleeding. The duodenum and upper jejunum were very congested and hæmorrhagic and in some cases showed definite circumscribed pre-ulcerated areas, which could be seen on the serous surface. The spleen and pancreas were congested; the liver appeared fairly normal. In D 81 the heart appeared dark and mottled on both surfaces; in other animals the outer surface of the heart appeared normal. Infarcted areas were observed in some of the papillary muscles. The auriculo-ventricular valves were congested and hæmorrhagic, particularly on the auricular side of the valve. The outer surface of the aorta in the region of the deep and superficial cardiac plexuses appeared congested.

Microscopic examination.—Congestion in the gastric and intestinal mucosa and submucosa was noted. The liver, kidney and pancreas all showed definite evidence of congestion.

Numerous areas of hyaline degeneration were observed in the heart sections taken from these animals. One of the sections showed hæmorrhagic areas about the small blood vessels, while others showed fibrous areas in the myocardium.

Scattered areas of hæmorrhage with infarcts were observed in the apex of the heart of D 83. The heart sections taken from D 89, the animal which received atropine in addition to stimulation, appeared normal.

GROUP II

Vagus stimulation in the eserinizd dog.—In addition to vagus stimulation these animals were given a continuous injection of dilute eserine through the external jugular vein. A combination of the continuous injection apparatus (Manning and Hall, 1937) with the slip-ring-contact (referred to previously) was used. By means of this apparatus both continuous stimulation and intravenous injection were carried out for 41 to 50 hours, and in one instance for 72 hours, during which time the animal was free to move about its cage. The eserine solution was injected at a rate of 200 c.c. per hour and the concentration regulated so that the animals received 0.05 mg. of eserine every 30 minutes. This amount was found to markedly inhibit the choline-esterase activity.

Throughout the course of these experiments vomiting and diarrhœa occurred. These effects, at first slight, later became more severe. The vomitus became very foul and in one case contained bloody bile-stained material. In addition to the diarrhœa, melœna was observed towards the termination of the experiment. As in the animals in Group I, exophthalmos of the left eye occurred and became more pronounced as the experimental time progressed.

Autopsy report.—The animals appeared to be well nourished. The lungs were fairly normal, with some evidence of slight congestion. The heart appeared dilated, the pericardium œdematous and slightly hæmorrhagic. No gross lesions were observed on the outer surface of the heart except in one case where the apex appeared dark. On opening the heart sub-endocardial hæmorrhage was observed. One animal showed papillary muscle congestion, while another revealed numerous blood clots adherent to the endocardial surface.

In all cases the urinary bladder was small, contracted and empty. The outer surface appeared hæmorrhagic and the mucous membrane œdematous and congested. Congestion was apparent in the kidneys of two animals. There were indications of some fibrotic areas in the

spleen. The liver appeared slightly pale but was otherwise normal.

The upper gastro-intestinal tract appeared congested and hæmorrhagic. In one animal definite ulcerated areas were seen in the pylorus and three similar areas in the duodenum. In another, areas of severe irritation which showed through to the serous surface were observed in the duodenum and stomach. In one animal marked extravasation of blood into the tissue spaces and between the muscle layers (noticed particularly between abdominal muscles) was noted.

Microscopic examination. — Sections taken from these animals showed marked congestion in the liver. Necrosis of the central vein area was observed in some. The kidney and spleen also appeared congested. Marked congestion with hæmorrhage was observed in the pylorus and duodenum, and in some of these sections areas of ulceration were noted.

The heart sections revealed a considerable degree of capillary congestion and hæmorrhage. Hyaline degeneration of the myocardium was noted in all instances. Myocardial degeneration was more marked in this group (vagus stimulation and eserine) than those which had received vagus stimulation alone.

CONCLUSIONS

By means of continuous vagal stimulation (31 to 45 hours) it has been possible to produce a mild degree of myocardial damage in dogs under light nembutal anaesthesia. When the choline-esterase of the blood was inhibited by the frequent injection of eserine more marked myocardial damage was found, and in addition definite peptic ulceration occurred. Since no myocardial or gastro-intestinal damage was noted, atropine apparently, by its effect on the parasympathetic nervous system, protected the animal from the effects of vagus stimulation for long periods of time (70 hours).

When vagal stimulation was carried out on unanaesthetized and unrestrained dogs greater total stimulation was possible (70 to 90 hours, and in 2 instances 120 hours). With this increase in the length of stimulation time more marked myocardial damage was produced. Again, the animal which received atropine in addition to vagus stimulation not only survived

the treatment twice as long (160 hours) as the others but showed no evidence of myocardial damage. The group which received eserine in addition to continuous stimulation showed definite evidence of peptic ulceration in addition to more marked evidence of myocardial damage.

When these results are considered together with those of Hall, Ettinger and Banting (1936) the original hypothesis is more definitely established, namely, that parasympathetic over-excitation through liberated acetylcholine results in myocardial damage. Furthermore, the occurrence of gastro-intestinal disturbances appears to be related to an exaggerated vagal tone. Such changes are the result of a more acute disturbance of autonomic equilibrium.

SUMMARY

1. Myocardial damage is initiated by prolonged vagal stimulation under light nembutal anaesthesia.
2. The occurrence of myocardial damage due to prolonged stimulation of the vagus nerve is prevented by atropine and accentuated by eserine.
3. Stimulation of the vagus nerve in the unanaesthetized dog results in a greater degree of myocardial degeneration than in the lightly anaesthetized animal.
4. Areas of duodenum and pylorus show marked congestion and hæmorrhage following prolonged vagal stimulation. These effects are abolished by atropine and accentuated to the extent of ulcer formation by eserine.

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THE DIAGNOSIS OF COMMON CAUSES OF JAUNDICE*

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JAUNDICE implies a staining of tissues and body fluids with bilirubin. It is a symptom rather than a disease and represents nothing more specific than an accumulation of physiological waste. It is well known that bilirubin is passively excreted by the liver, the pigment itself being formed in the reticulo-endothelial system; an excess of bilirubin in the blood and tissues, therefore, may result from one of the following causes: (1) an increased rate of destruction of hæmoglobin and production of bilirubin beyond the capacity of the liver to eliminate it; (2) a "block" in the hepatic filter, which results from toxic or infectious injury of the hepatic cells, and (3) mechanical interference with the flow of bile through the extrahepatic channels. Following McNee's classification, these three varieties of jaundice may be designated, respectively, as hæmolytic, hepatogenous (toxic or infectious), and obstructive. A similar classification which has been proposed by Eppinger is as follows: (1) mechanical jaundice (intermittent, partial, or total), and (2) non-mechanical jaundice (pleochromic, hepatosplenic, or hepatogenous). For purposes of the discussion to follow the former classification will be used. No matter which is employed, it is well to recall Rich's statement that jaundice depends fundamentally on the balance between the amount of bilirubin delivered to the liver and the capacity of that organ to excrete it.

For practical purposes clinicians are interested in determining whether jaundice is due primarily to a blood dyscrasia, to hepatocellular injury, or to mechanical interference with biliary flow, a differentiation which may sometimes be difficult, since there are probably no strictly "pure" forms of jaundice. Depth, duration, and constancy of bilirubinæmia depend on the following variable factors: (1) the rate of destruction of erythrocytes; (2) the completeness of biliary obstruction, and (3) the rate of

hepatic parenchymal damage. Unfortunately, these are not to be measured by any but the most indirect methods. It is also true that jaundice of any type is not static and that the individual factors which modify its course are constantly changing. Consequently, physicians are, at most, able to recognize only the dominant factor in the individual case at the time at which it is observed.

THE DATA NECESSARY FOR DIAGNOSIS

With these conceptions in mind, one may turn to the gathering of data necessary for diagnosis. In most cases no elaborate laboratory equipment is necessary, and clinical judgment should supersede any supposedly pathognomonic sign or infallible laboratory procedure. The first necessity is, of course, an adequate chronological history, with special reference to pain, its character, situation, and mode of relief as well as its relation to the appearance of jaundice. Emphasis is also to be placed on any antecedent history of dyspepsia, systemic disease, or exposure to hepatotoxic substances. Physical examination should be complete and painstaking; a study of the colour of the skin may be helpful in distinguishing the lemon yellow hue of hæmolytic icterus from the orange jaundice due to primary hepatic injury and from the greenish cast of the skin so commonly seen in the presence of obstructive processes.¹ A factitious dermatitis speaks for pruritus, which usually is present in its most aggravated form in cases of malignant biliary obstruction. A search for metastatic involvement of lymph nodes should be made, and abdominal scars should be inspected for evidence of previous fistulous tracts. Examination of the abdomen should include not only a determination of the size and consistency of the liver, spleen, and gall bladder but a search for other organs or masses; it may be facilitated by immersion of the patient in a tub of hot water or by the administration of a sedative. The next step is to determine the patency of the biliary passages. To inquire about the colour of the stools is of

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little value, since the excessive amount of fat present in the stools of the icteric patient masks the colour of bile pigment. A chemical test for bile in the stools is a necessity, and in case of doubt duodenal intubation should be employed to settle the question. Remembering the variable nature of benign mechanical obstruction, the presence or absence of bile in the intestinal tract should be checked repeatedly in cases in which the diagnosis is uncertain. The depth and variability of jaundice is the next consideration. A van den Bergh test will clarify the problem by determining whether the reaction is direct or indirect; if it is indirect the jaundice is certainly due to some hæmolytic processes; if direct, obstructive and hepatogenous types of jaundice will have to be distinguished one from the other. The day-to-day fluctuations in jaundice, as well as its relative degree, may be determined either by the values for the serum bilirubin or by the icterus index. Deep, constant jaundice usually means severe acute hepatic injury or malignant obstruction; low variable bilirubinæmia is commonly associated with benign obstructive lesions and with the more chronic forms of parenchymatous liver disease. The necessity for following the course of jaundice is apparent, since this may, and frequently does, enable one to determine the prognosis and the time at which surgical intervention may be carried out with greatest safety.

The various tests for liver function may be considered last. During the past several years numerous procedures have been devised to determine whether or not jaundice is primarily obstructive or hepatogenous in origin in a given case. All of these tests are based on two facts: (1) early in the course of biliary obstruction, the blood may contain substances (other than pigment and bile salts) which are forced into circulation because of mechanical interference with biliary flow, and (2) the liver itself is not much disturbed early in the course of obstructive jaundice, while in hepatogenous jaundice there are frequently early and serious disturbances of some of its essential functions. It is agreed that hepatic parenchymal injury always follows biliary obstruction and, in fact, may appear early and greatly confuse the clinical picture. On the other hand, obstruction may be incomplete and of such short duration as to produce little change in the composition of the blood. In hepatogenous jaundice functional

disturbances may be difficult to detect, since the initial injury may be quickly repaired and may produce little evidence of dysfunction. For these reasons, all of the various differentiating tests must be used with the time-element in mind; in uncomplicated forms of jaundice of short duration, clear-cut results may be obtained but there is a large margin of error in cases of very chronic jaundice. A brief statement in regard to these tests and other laboratory data useful in the diagnosis of jaundice seems desirable.

Cholesterol and cholesterol esters.—The concentration of these normal components of plasma and bile is ordinarily increased in obstructive jaundice in rough proportion to the completeness of obstruction; as infection and biliary cirrhosis complicate the picture the value for the plasma cholesterol decreases. In cases of primary hepatic injury, decreased or normal values for the plasma cholesterol prevail; the value for the cholesterol may decrease and the cholesterol esters may virtually disappear from the plasma in cases of severe acute hepatic injury.⁷

Phosphatase.—Phosphatase normally is present in bile and serum. The concentration in the blood may be increased because of obstruction to the biliary flow; values greater than 35 units per 100 c.c. of serum are characteristic of obstructive jaundice. Normal or decreased values are the rule in cases of hepatogenous jaundice.²³ There unfortunately is a large number of cases in which intermediate values are obtained (10 to 35 units per 100 c.c. of serum); in such cases differentiation on this basis is difficult or impossible.

Serum proteins.—With advancing hepatic injury a decrease in the value for the serum protein and a reversal in the albumin-globulin ratio are the rule. These changes develop rather late in cases of obstructive jaundice unless there has been some antecedent injury of the liver; the most striking alterations are seen in cases of parenchymatous disease of the liver.

Galactose.—Normal tolerance for galactose is the rule in cases of early obstructive jaundice. In many (20 to 40 per cent) of the cases in which jaundice is advanced and associated with gallstones, stricture of the common bile duct, or carcinoma, the tolerance for galactose is decreased.²⁷ In cases of severe acute parenchymal injury of the liver a marked decrease in the

tolerance for galactose is diagnostic; however, galactose tolerance may improve with the passage of time and is usually normal in cases of cirrhosis of the liver.

Hippuric acid.—The hippuric acid test is based on the detoxifying function of the liver and its ability to effect a synthesis of benzoic acid and glycine.²² The results are roughly comparable to those of the galactose tolerance test, but the ability of the liver to form hippuric acid is definitely a more sensitive indicator of hepatic injury in the presence of biliary obstruction. The test has the disadvantage of being affected by renal insufficiency and is not reliable in the presence of an increase in the value for blood urea or a reduced urea clearance.

Urobilinogen and urobilin.—Urobilinogen is formed by the action of intestinal bacteria on bilirubin; urobilin is one of the oxidation products of bilirubin. As F. Müller observed years ago, urobilinogen is purely enterogenous; it is normally absorbed from the intestine and returned to the liver; little or none of it appears in the urine. If no bile reaches the intestine, naturally no urobilinogen can be formed; if its formation is normal and the liver cannot reabsorb it it appears in the urine in quantities which are more or less directly related to the degree of hepatic injury. There are many angles to the problem which are beyond the scope of this paper; suffice it to say here that absence of urobilinogen from the urine of a jaundiced patient argues for complete biliary obstruction, while an excess of urobilinogen usually signifies patent bile ducts and injury of the liver. To study the problem adequately in an individual case quantitative determinations of urobilinogen and a consideration of the ratios in the urine and faeces are essential, as Watson has shown. The result of a single test is to be taken with reservations but may occasionally be helpful.

Accessory laboratory procedures.—Of these the one which most often is attempted is a cholecystogram, but it is by all odds the least useful test, since the dyes used are handled by the liver no better than is the bilirubin that already is present in the blood. An ordinary roentgenogram of the region of the gall bladder may reveal stones or a primary shadow, and thus furnish valuable information. Hepatography following the administration of thoro-

trast will detect metastatic malignancy but it is rarely necessary. A study of the formed elements of the blood is important, since a leukocytosis or a macrocytosis may be of diagnostic significance. In cases of hæmolytic jaundice, studies of the morphology and fragility of the erythrocytes are of great value. A Wassermann reaction is an obvious requirement, since it may give the clue to a syphilitic hepatitis or an arsphenamine jaundice.

FREQUENCY OF THE VARIOUS TYPES OF JAUNDICE

The statistical distribution of the causes of jaundice is of some academic interest. As Hartman's figures show, about 25 per cent of jaundiced patients have gallstones or associated conditions; this group includes patients who have stones in the common bile duct, cholangitis, and pancreatitis, singly or in combination. In a slightly larger percentage (30 per cent) of cases, carcinoma is responsible for jaundice; metastatic carcinoma as well as neoplasms of the pancreas, gall bladder, and bile ducts figure in this total. In still another 25 per cent the lesion which causes jaundice is confined to the parenchyma of the liver; both acute and chronic forms of jaundice, whether toxic or infectious, are included here. In from 7 to 10 per cent of all cases of jaundice there is a hæmolytic form of icterus, and in about the same percentage the jaundice is the result of a benign stricture. In the small remaining percentage the jaundice is chiefly due to rare obstructive lesions such as cysts and extrabiliary tumours. Since hæmolytic icterus and stricture are as a rule readily identified and excluded from consideration, it appears that in the remaining cases there are two chances in three that in any given case the jaundice is obstructive; likewise, there is one chance in three that a "curable" or removable benign lesion will be present, and an equal chance that a neoplasm will be found. The common lesions which cause biliary obstruction develop chiefly in middle life or later life, whereas the commonest type of jaundice which affects young persons is due to hepatocellular damage. The sex factor may also be mentioned; statistically, an obstructive type of jaundice which affects a woman is most likely caused by a gallstone, while if the patient is a man the chances of neoplastic obstruction are distinctly greater.

HÆMOLYTIC FORMS OF JAUNDICE

Hæmolytic icterus, by definition, depends on an increased formation of pigment because of accelerated destruction of erythrocytes. In the normal person it would seem to be difficult, if not impossible, for the excretion of bilirubin to exceed the physiological levels, since a very small amount of liver (5 to 10 per cent) will meet all ordinary requirements for disposal of the pigment. The bilirubinæmia of hæmolytic icterus is thus difficult to explain, since most patients who have hæmolytic forms of icterus have no demonstrable injury of the liver. However, practically all known forms of hæmolytic icterus may be associated with anæmia and anoxæmia, which may of themselves depress hepatic function.

The essential clinical features of the hæmolytic types of icterus are: (1) an indirect-reacting serum bilirubin; (2) acholuria; (3) an increase in the amount of urobilin in the urine and fæces, and (4) splenomegaly and evidence of destruction of blood. The perfect example of hæmolytic icterus is presented by the typical familial form, a definite and well recognized disease entity. The pathognomonic feature of this disease is, as Naegeli first emphasized, the presence in the blood of fragile spherical microcytes. These cells may comprise 10 to 25 per cent of all erythrocytes and are directly responsible for the observed increase in the fragility of the erythrocytes. Apparently, the spleen is the specific locus for the destruction of these microcytes, and because of this splenectomy is a curative procedure. The formation of microcytes, however, is not affected, and these cells have been found in blood smears many years after splenectomy.³ In some families which have been studied these cells have also been demonstrated long before hæmolysis became active.

There are other rather common varieties of symptomatic hæmolytic icterus, such as the physiological icterus of the newborn,⁴ that seen after the administration of phenylhydrazine, and that associated with pernicious anæmia and sickle-cell anæmia. Less common types of hæmolysis and bilirubinæmia are those associated with malaria, paroxysmal hæmoglobinæmia, hæmolytic septicæmia, and the transfusion of the wrong type of blood; a specific type of hæmolytic anæmia which is associated with hepatic

cirrhosis also has been described. After all these causes of jaundice have been excluded there still remains a group of atypical hæmolytic anæmias which are characterized by acholuric jaundice, regenerative types of anæmia, and splenomegaly. Thompson's report of a series of 15 such cases emphasizes that the principal point of differentiation is the absence of spherical microcytosis and a normal fragility of erythrocytes. In this series of cases 3 patients had a reticulated cell sarcoma of the spleen, and one patient died of tuberculosis of the spleen. Two had syphilis, and antisymphilitic treatment cured the hæmolytic tendencies; 4 other patients were subjected to splenectomy but this did not produce any improvement.

The diagnosis in hæmolytic icterus can be summed up by saying that there are three general forms of this condition: (1) a specific familial disease in which there is a characteristic blood picture; (2) a similar type without the characteristic blood picture; and (3) a miscellaneous type which is associated with other distinctive disease syndromes; in this type the hæmolytic icterus is only an incidental finding. If the morphology of the blood and the indirect-reacting serum bilirubin are borne in mind, diagnosis should cause little difficulty except in the presence of the following conditions: (1) acute hæmolytic crises; (2) atypical hæmolytic anæmia, and (3) familial hæmolytic icterus associated with gallstones and obstructive jaundice. Since more than 50 per cent of patients who have the familial form of the disease eventually have pigmented gallstones this possibility must always be kept in mind.

HEPATOGENOUS JAUNDICE

The so-called intrahepatic types of jaundice depend on a regurgitation of bile through ruptured bile capillaries, a phenomenon which in turn is caused by degenerative or inflammatory lesions of the hepatic parenchyma. The acute conditions are analogous to the acute forms of nephritis; the chronic varieties are analogous to the contracted kidney. As is the case in renal disease transitions from the acute to the chronic form are noted, while the pathological changes and the degree of functional impairment are not necessarily parallel.

The essential clinical features to be emphasized are the absence of pain, the patency

of the bile passages, and the presence of bile and urobilinogen in the urine.

Among the types of hepatogenous jaundice most frequently seen are the epidemic or catarrhal jaundice, the toxic forms which are secondary to drugs and poisons, and toxic hepatitis which occurs in the course of systemic disease. The general clinical picture produced by all these types is much the same, no matter what the etiological agent. The onset of symptoms is usually gradual and painless. The symptoms include anorexia, nausea, vomiting, diarrhoea, slight fever, and general malaise. Jaundice appears insidiously; it is not, as a rule, followed by pruritus; the urine is dark and the stools are clay-coloured at first; both show a more normal colour as the disease advances. The liver is often somewhat enlarged and tender on pressure; in at least one case out of four the tip of the spleen can be palpated. Examination of urine for pigments shows less bile than one would expect with the observed degree of bilirubinæmia; urobilin and urobilinogen are present in normal or increased quantities. The stools are rarely acholic for any length of time; the duodenal contents eventually contain a moderate quantity of bile as well as mucous plugs and material resembling casts. As mentioned in an earlier paragraph, the tolerance for galactose is diminished and the concentration of cholesterol in the plasma is reduced in cases in which the condition is moderately severe.

Certain of the individual types of acute hepatitis have distinguishing features which deserve comment. Catarrhal jaundice is by all odds the commonest of all diseases associated with icterus. Its etiology is unknown but it behaves in some respects as an infectious disease; local epidemics are relatively common. Leukocytosis may be noted at the onset, while a leukopenia has been described in the later stages. Jolliffe has considered the condition as a specific entity and divided its course into three stages: (1) an obstructive phase associated with complete acholia which lasts, on an average, for eleven days; (2) a critical phase of approximately four days' duration, which is characterized by a sharp decrease in the value for the serum bilirubin; (3) a period of recovery which lasts about nine days; in this period the value for serum bilirubin decreases

and the bile disappears from the urine. It is not certain that the disease will always follow such a scheduled course, nor indeed that it is a disease entity at all; one sees many cases in which the condition appears to be "catarrhal" jaundice at the onset, but a very chronic form of hepatitis develops, and such complications as ascites and oedema may occur.³⁴ Even in the ordinary form of the disease tests for liver function which are performed months after recovery supposedly is complete may show definite residual injury. Doubtless, many different etiological agents figure in these supposedly infectious varieties of hepatogenous jaundice and the course and prognosis vary accordingly.

Arsphenamine jaundice usually occurs during the course of arsphenamine treatment of recent syphilis, but it is not necessarily related to the amount of the drug given or to the stage of the disease. The earlier the appearance of icterus after the last injection of arsphenamine, the more benign, as a rule, is the course of the condition; when icterus develops late it may be associated with severe and lasting hepatic injury. Clinically, the condition closely resembles catarrhal jaundice, but it is likely to be of longer duration and serious sequelæ are more frequent. Diagnosis may be difficult, especially if the patient desires to conceal the primary condition.

Toxic jaundice caused by cinchophen.—The idea of a specific type of injury of the liver caused by cinchophen has not received the attention that it warrants. The condition is common and exceedingly serious; the mortality is about 50 per cent.³⁵ The danger lies not so much in the case in which the patient uses cinchophen compounds under the direction of a physician as it does in the case in which he uses a patent medicine of unknown composition. The acute forms of cinchophen jaundice are almost invariably accompanied by complete relief from the symptoms of arthritis, and the patient is therefore inclined to welcome this relief, to attribute it to the drug, and to overlook the minor discomfort of jaundice. These errors have led to many fatalities.

There are about 80 or 90 antirheumatic remedies which contain the toxic quinoline radical, many of which are readily obtainable

under various trade names. The chances that any patient will be affected are small, perhaps 1 in 250,000 or less, but it is likewise true that a susceptible person may be injured by only a few grams of a product which contains cinchophen, while the "immune" person may take such drugs for years without demonstrable harm. Among other hepatotoxic drugs which produce jaundice must be mentioned chloroform, carbon tetrachloride, yatren (iodoxyquinoline sulphonic acid), dinitrophenol, and the gold salt, sanocrysin. There are also numerous compounds used in industry which may produce similar effects; the most recent addition to the list is dimethylnitrosamine.⁸

The chronic forms of hepatitis and jaundice are poorly understood and their etiology is obscure; the so-called hypertrophic biliary cirrhosis of Hanot is only a convenient catch-basket for a variety of hepatic lesions.³⁶ This syndrome probably represents an advanced stage of hepatitis with periportal fibrosis and regeneration and includes at least four types of cases: (1) obstructive biliary cirrhosis secondary to intermittent partial obstruction of the bile passages; (2) chronic infectious types of cirrhosis which develop as a result of previous systemic disease or because of chronic infectious processes elsewhere in the gastrointestinal tract (chronic ulcerative colitis, low grade chronic infectious lesions of the gall bladder and pancreas); (3) certain forms of chronic atrophy of the liver, and (4) a type of familial hepatic dysfunction associated with low-grade hyperbilirubinemia, which may eventually progress to chronic hepatitis and definite clinical jaundice.²⁵

There are certain clinical features common to all of the chronic forms of hepatitis. Jaundice is, as a rule, slight and fairly constant and the bile passages are patent. Pruritus and a thickened melanotic skin are common developments. The liver is ordinarily symmetrically enlarged and firm, and splenic enlargement is the rule. Curiously enough, there is relatively little evidence of hepatic insufficiency even in cases in which the condition has been present for a long time; many patients live for years in moderately good health. The ultimate outcome is unfavourable, although numerous recoveries are on record.

OBSTRUCTIVE JAUNDICE CAUSED BY BENIGN LESIONS

The distinguishing features of jaundice caused by benign obstructive lesions are pain, variable jaundice associated with intermittent patency of the bile passages, choluria, and progressively increasing injury of the liver.

Stones in the common bile duct.—The signs and symptoms presented by the majority of patients who have stones in the common bile duct are too familiar to require detailed consideration. Approximately three-fourths of all patients suffer from attacks of biliary colic followed by transient slight jaundice, chills, fever, and residual soreness in the upper part of the abdomen. At least a fourth of all patients with common duct stones have been subjected to previous operations on the biliary tract. As many surgeons have noted, the number of stones that are found in the common bile-duct depends almost entirely on the frequency with which the duct is opened and explored. If one reviews the histories of a series of cases in which stones were found in the common bile-duct, one will note two striking points: (1) the most common symptom is persistent indigestion with specific intolerance to certain types of food, and (2) the accounts of colic in an individual case vary greatly, and in at least 15 to 20 per cent of cases the pain may be atypical in character and situation, while in about 5 per cent the condition is entirely painless. In some patients the pain may bear no relationship to the onset of jaundice, and it is not unusual to encounter an individual who has been jaundiced for some time before experiencing any pain whatsoever. One occasionally encounters patients who have neither jaundice nor pain but have only recurrent febrile attacks which are associated with nausea and vomiting. There is another remarkable group of patients, described years ago by Osler, in which pain is present but not the outstanding feature; the principal clinical finding is long-standing, variable jaundice which simulates parenchymatous disease of the liver or malignancy.

It is significant that stones rarely, if ever, completely occlude the common bile duct for any length of time. For this reason the stools and duodenal contents always contain bile at

one time or another, and jaundice is as a rule slight and variable. If no complicating lesion of the liver is present the average value for the serum bilirubin is about 5 mg. per 100 c.c.; in the presence of cholangitis and biliary cirrhosis, higher values (10 mg. per 100 c.c.) are the rule.²⁶ There also may be rapid fluctuations in the values for the serum bilirubin, particularly after an episode of pain; these fluctuations are rarely seen in any other type of jaundice and are almost diagnostic of a stone.

A good deal of attention has been paid recently to the presence of jaundice in cases where gallstones are confined to the gall bladder and cystic duct. Hartman has described a series of such cases in which there was either jaundice at the time of operation, or a history of it, without evident calculous obstruction of the bile ducts. In approximately three-fourths of these cases inflammatory changes in the liver, pancreas, or extrahepatic passages, and enlarged contiguous lymph nodes or local inflammatory reactions in the bile passages were found at operation. The relationship of pancreatic oedema or inflammation to the production of jaundice is important in such cases; a sharp increase in the icterus index may develop during an acute pancreatitis, while in the more chronic types of interstitial pancreatitis deep constant jaundice may be present and simulate malignant obstruction.

Pancreatitis is perhaps a less frequent cause of jaundice than is the hepatitis which so frequently accompanies cholecystic disease. Many authors, notably Graham and his co-workers, and, most recently, Klopp and Cantarow, have noted the frequency with which either calculous or non-calculous cholecystitis may produce jaundice because of hepatitis, cholangitis, pancreatitis, and (hypothetically) spasm of the sphincter of Oddi. The same authors also have noted the frequency of a direct van den Bergh reaction and subclinical jaundice after an attack of biliary colic, and have commented on the fact that there may be retention of bromsulphalein for several days following such an attack.

Benign stricture of the common bile duct and hepatic ducts.—Stricture of the common bile duct rarely occurs spontaneously; in the over-

whelming majority of cases it follows cholecystectomy. The usual history is that of post-operative development of jaundice, external biliary fistula, or both. In many cases the condition probably is directly attributable to surgical trauma which, as Walton has pointed out, may easily occur because of anatomic variations in the extrahepatic ducts, because of adhesions between the cystic duct and common bile duct, and because of attachments of Hartman's pouch to the common bile duct itself. In most examples of this condition jaundice develops within a relatively short period of time after the original operation; there are other cases in which it may be a late development, supposedly because of the development of an obliterative cholangitis.

The symptoms of stricture obviously depend on the duration and completeness of biliary obstruction and the degree of hepatic injury. Pain is not uncommon but rarely reaches the proportions of a true biliary colic. There is often dull aching distress, exacerbations of which may be followed by chills and fever. Pruritus is common and severe. Jaundice is rather constant; the value for the serum bilirubin averages about 10 mg. per 100 c.c., and in approximately 80 per cent of cases there are small amounts of bile in the duodenal contents. Because of the combination of biliary obstruction and infection, biliary cirrhosis and splenomegaly develop early. These complications do not necessarily contraindicate operation, but obviously increase the surgical risk and prolong convalescence. Even after the most technically perfect reconstruction of the bile ducts, recurrence of the stricture may take place but in spite of this surprisingly good results have been reported.

Malignant obstruction of the bile passages.—

The clinical features common to all forms of malignant biliary obstruction are related to its completeness and permanence. The most common type of malignant obstruction of the bile passages is that caused by carcinoma of the head of the pancreas. This develops in late adult life; males are more commonly affected than are females. In about 40 to 50 per cent of cases the patients have no pain whatever; in about 25 per cent there may be vague or intermittent colicky pain, but in the remainder

dull aching discomfort is the rule. In many cases the pain extends across the upper part of the abdomen to the left side and may be felt even in the left subscapular region. The jaundice produced by carcinoma of the pancreas is deep and remarkably constant; the average value for the serum bilirubin level is 17 mg. per 100 c.c. Much higher values are often recorded, and, in fact, the maximal degrees of bilirubinæmia are seen in neoplastic obstruction and in the more severe forms of hepatogenous jaundice. Complete acholia is the rule; even repeated duodenal intubation reveals no trace whatsoever of bile. Bloody mucous plugs and even gross hæmorrhage may be detected by duodenal drainage; these are of diagnostic significance.² In about 25 per cent of cases the tumour may occlude the pancreatic duct; under these circumstances, fatty diarrhoea may develop for obvious reasons. The gall bladder is greatly distended and should be palpable in a high percentage of cases (60 per cent); a comparable distension of the whole duct system also follows.

There are certain laboratory tests which give useful confirmatory evidence in diagnosis and aid in distinguishing the condition from other painless forms of jaundice. In the early stages of the condition a high concentration of cholesterol in the plasma, an increased value for serum phosphatase, and a negative galactose tolerance test are usually noted. As hepatic injury from hydrohepatosis increases the results of these tests may be reversed. Inasmuch as no bile enters the intestinal tract, urobilin and urobilinogen will be absent from the urine. A roentgenogram of the stomach and duodenum may reveal duodenal deformities or even pressure on the pyloric antrum.

Tumours of the common bile duct, cystic duct, and hepatic duct are of more academic than clinical interest. A favourite site for such tumours is the lower end of the common bile duct; a lesion situated there, even if of small size, produces complete obstruction. The clinical symptoms are essentially identical with those of pancreatic cancer. In more than half of the 53 cases reported by Marshall there was associated benign cholecystic disease, but in spite of this there was rarely any marked degree of pain. The correct pre-operative diag-

nosis is rarely made; one may suspect a tumour of one of the ducts in cases in which there are some signs of pancreatic carcinoma but in which the gall bladder cannot be palpated. In a few cases it has been possible to resect the affected portion of the duct, but, as a rule, the condition is inoperable. Malignant tumours of the gall bladder itself may also involve the common bile duct and produce obstructive jaundice. The symptoms of the condition are extremely variable, but when jaundice occurs it is deep and constant; there is often a fixed hard mass in the right upper quadrant of the abdomen.

The hydrohepatosis which results from all types of malignant obstruction is extreme and, if unchecked, will produce irreparable hepatic injury. Curiously enough, the condition may be tolerated for a time by certain patients but in other cases the disintegration of the liver seems to progress at a more rapid rate. The sudden development of the hæmorrhagic diathesis and hepatic insufficiency may occur spontaneously or follow surgical procedures, a fact which accounts for the high operative risk.

COMMENTS ON TREATMENT, WITH SPECIAL REFERENCE TO SURGICAL RISK

Of the three varieties of hæmolytic jaundice only the specific familial type can be summarily cured by splenectomy. As Doan and Curtis have demonstrated, the operation may be performed with comparative safety even during periods of acute hæmolysis. In the symptomatic forms of hæmolytic jaundice and in the atypical hæmolytic anæmias supportive medical treatment is about all that can be offered. Some care should be taken in giving blood transfusion, since hæmolysis may sometimes be aggravated by this procedure.

In the hepatogenous varieties of jaundice the prime requisite is the detection and removal of hepatotoxic substances, a desideratum not often accomplished. Therapy otherwise is best confined to building up the stores of glycogen in the liver; high carbohydrate diets low in protein and fat, such as those described by Tannhauser, may be recommended. The intravenous administration of dextrose is a requisite form of treatment in cases in which the condi-

tion is severe; as Chester Jones has shown, it is the best available method of preventing and treating hepatic insufficiency. Cholagogues, duodenal drainage, diathermy to the liver, and parenteral administration of liver extract have been recommended but their effects are doubtful. Most of the common forms of epidemic jaundice are self-limited and usually disappear in about six weeks; if arsphenamine, alcohol, or cinchophen can be incriminated the course may be somewhat more prolonged. In case of doubt it is well to consider jaundice hepatogenous until proved otherwise, or at least until the six weeks' interval has passed. The supportive treatment which has been mentioned should be carried out and close observation of the patient should be continued.

If jaundice is the result of mechanical obstruction, surgical intervention is indicated. It is the usual practice of a surgeon to explore the bile passages, regardless of the clinical syndrome present, in cases of painful variable jaundice, in cases of complete biliary obstruction, and in cases in which patients are known to have stone. There are other surgical indications, and in cases in which the diagnosis is uncertain, as it is in certain cases of chronic painless jaundice, exploration may be indicated. The problems of the internist, when operation is contemplated, are twofold; he should determine the probable risk and aid in the selection of a favourable time for operation. No infallible method of encompassing either of these objectives is known, and rule of thumb must serve in many instances. It is generally recognized that in the acute stage of obstruction the risk may be increased, and that in a case in

which the value of the serum bilirubin is increasing rapidly the patient is best treated conservatively until stabilization occurs. Once the acute stage is past, the danger signals to be noted are deep constant jaundice, fever and wasting, lethargy, stupor, or signs of cerebral irritation, a decreasing output of urine (which often is the first sign of renal insufficiency), and a hæmorrhagic tendency shown by studies of blood coagulation or by the appearance of purpura. Laboratory evidence of impending hepatic insufficiency, which often has to be heavily discounted, includes: (1) a concentration of serum bilirubin in excess of 20 mg. per 100 c.c.; (2) a decreasing value for the cholesterol and a disproportionate decrease in the cholesterol esters in the plasma; (3) an increasing sedimentation time; (4) an increase in the value for the blood urea, and (5) decrease in the excretion of hippuric acid.^{28, 31} It should be emphasized that there are few absolute contraindications to operation in cases of obstructive jaundice. The problem is that of considering the probable risk against the possible benefits, and in this field the experience of a competent surgeon is the best guide. If, as Moynihan has said, no man is infallible in diagnosis, it must be admitted that prognosis is equally subject to error. However, increasing accuracy in diagnosis, better selection of patients, and adequate pre-operative care have gone far to make the surgical treatment of jaundice a safer and more certain matter than at any time in the past.

An extensive bibliography has been prepared and may be had on application to the author. The numbers in the text refer to the papers quoted.

PRONTOSIL IN ERYSIPELAS.—K. Motzfeldt reports from a hospital in Oslo his experience in the treatment of erysipelas. In the pre-prontosil period 1924-35 there were 176 patients, of whom 106 were women. The average age was 34, and there were 12 deaths, an average mortality of 6.8 per cent. Three out of 9 patients under the age of 1 and 2 out of 8 over the age of 70 died; the average duration of the fever was nine days. Except for 10 cases given a supposedly specific serum, the patients in this group received only symptomatic treatment. In the prontosil group there

were 20 patients, all of whom, with only one exception, suffered from erysipelas of the face. The prontosil was given simultaneously by the mouth and by intramuscular injections. In every case the temperature fell to normal within two days after the first administration of prontosil, and the average duration of the fever in this group was between three and four days. The rash disappeared very quickly, the improvement in the general condition was remarkable, and there were no deaths.—*Norsk. Mag. Laegevidensk.*, June, 1937, p. 630. Abs. in *Brit. M. J.*

JAUNDICE: SURGICAL CONSIDERATIONS*

BY A. T. BAZIN

Montreal

DR. MAGNER and Dr. Snell have expounded the normal and pathological physiology of bile excretion, the variety of causative factors in the development of jaundice, the differential diagnosis, and the indications for varying types of treatment. It falls to my lot to present the problem from the surgeon's point of view.

First I wish to emphasize that the surgeon who desires intelligently to undertake the care of these jaundiced patients must know at least the fundamentals, if not the details, of the knowledge contained in the papers of the two men who have preceded me.

Familial hæmolytic jaundice.—The only type of hæmolytic jaundice which benefits from splenectomy is the *familial* type of the disease. Diagnosis must be carefully arrived at by scrupulous attention to the blood morphology and behaviour, in order to eliminate simulating conditions which not only do not benefit from splenectomy but in which splenectomy will actually be harmful. Given a true case of familial hæmolytic jaundice, the operative procedure is the easiest of all the splenectomies. The organ is not unduly enlarged, is soft and easily moulded to deliver through a comparatively small incision; there are no adhesions and the vessels of the pedicle are easily isolated for ligation.

In the hæmolytic crises which are prone to occur during the course of this chronic disease the splenectomy is no more difficult, but the patient's condition of profound anæmia is a cause for anxiety. Operation should be postponed if the patient responds at all satisfactorily to repeated blood transfusion. If operation becomes imperative the patient should be prepared by frequently repeated small transfusions, the operation performed at the optimum time as determined by hæmoglobin estimation, using as the anæsthetic ether with oxygen. As soon as the splenic pedicle has been secured a full 500 c.c. blood transfusion

is given and small transfusions repeated until the acute anæmia is combated. Ligation of the splenic artery in continuity is not here indicated as an alternative to splenectomy. In resorting to blood transfusion in hæmolytic jaundice special care in bloodmatching is required as further hæmolysis may be induced by even a minor mismatching.

The pitfall in familial hæmolytic jaundice is the very frequent occurrence of pigment stones in the biliary tract, usually in the gall bladder, but sometimes in the common duct. In the former position a biliary colic may ensue and the pre-existing jaundice may lead to the mistaken diagnosis of stone partially obstructing the common duct. With stone actually in the latter position the picture is confusing, as obstructive jaundice is superimposed upon the hæmolytic jaundice. But attention to the details of past history and a careful physical examination will clear the issue.

The question arises: Which condition should have priority in operative procedure, or may both operations be performed at the one time? My own opinion is that the splenectomy should be done first, and followed, after a reasonable time for convalescence, by operation upon the biliary system. Doing the two easy operations at one time was formerly my practice, but I had a death in one patient which simulated an acute "liver death" but may have been portal thrombosis; no autopsy was permitted.

Inasmuch as the hæmolysis is the cause of the deposition of the bile pigments as calculi it seems reasonable to deal with the spleen first, thus correcting the hæmolysis and allowing the bile to become less concentrated, washing down within reach any bile sand which may be intrahepatic. It must be remembered that this is a condition, perhaps the only one, in which formation of biliary calculi is not due to or related to biliary system infection. It therefore suffices to remove the stones, preserving the healthy gall bladder and even avoiding its drainage. Of course there are exceptions, as hæmolytic jaundice does not

* Being the third chapter of a Symposium on Jaundice, held at the Sixty-eighth Annual Meeting, Canadian Medical Association, June 23, 1937.

ensure against biliary infection. The two conditions may be associated although not related. Again, the very presence of small stones in the gall bladder predicates the presence of one or more in the common duct. There is therefore the necessity of most careful examination to ensure that the common duct is free.

Obstructive jaundice.—Depending upon the nature and site of the obstruction, surgical procedure attempts: (1) to remove the obstruction and restore normal continuity of the bile passages; (2) to detour the obstruction and lead the bile by indirect paths to the gastrointestinal tube; (3) to establish a biliary-cutaneous fistula to relieve intolerable itching and to prevent further hepatic damage; (4) in some few cases where the obstruction is at the hilum or intrahepatic the surgeon must retire in defeat. Hepato-cutaneous fistulae are of no avail.

There are two very real dangers in any operative procedure on a patient with obstructive jaundice: (1) the danger of continuous or recurring capillary oozing; (2) the danger of acute liver failure from the sudden relief of a long continued positive pressure in the bile ducts.

The danger of hæmorrhage can be guarded against. In obstructive jaundice of but a few weeks' standing there are certain alterations in the blood which lead to a delay in coagulation. In some obscure and as yet not completely explained manner this defective coagulability is associated with the relationship of calcium to the blood elements.

The practical points are: No operation should be undertaken upon a patient with obstructive jaundice until tests are made to ascertain the coagulation time, and pre-operative treatment has been successful in restoring the coagulation time to normal or nearly normal. Moreover, this pre-operative treatment must be continued as post-operative treatment until it is satisfactorily proved by repeated tests that the coagulation time remains constantly normal. If pre-operative treatment alone is carried out the surgeon may discover that after an interval of about four days following operation an oozing of blood will appear which will continue to a fatal ending in spite of the most active treatment then instituted. It would appear that prevention is the only effective method.

The treatment alluded to consists of the exhibition of calcium in large quantities by mouth or intravenously and repeated blood transfusions. Calcium may be given by the mouth but its absorption from the gastro-intestinal tract is uncertain. It is much more efficacious when given intravenously, and the salt we employ is the chloride; 5 c.c. of a 10 per cent solution, well diluted, are given on each of three successive days. On the last of these days a blood transfusion is given (500 c.c. gross of citrated blood). The coagulation test is then done, and, if satisfactory, operation is undertaken on the following day. If the coagulation test still shows a much delayed period the treatment is repeated.

Immediately after the completion of the operation another 500 c.c. of blood are given, and on each succeeding day the coagulation test is done, the reading of which is the guide to further courses of intravenous calcium and repeated small blood transfusions. The sedimentation rate test is used by some. It is an indirect test, and we feel is not as reliable as the coagulation test.

Occasionally conditions present in which it is advisable to do a two-stage operation. The first stage taps the biliary duct system proximal to the point of obstruction and establishes a biliary cutaneous fistula. The jaundice is then quickly relieved, blood coagulability is restored to normal, and a second-stage operation requiring extensive dissection and plastic restoration can be done with safety.

The second danger to which I have referred, *viz.*, acute hepatic damage with "liver death" due to sudden relief of long existent positive pressure, is probably more frequent than is suspected. I have vivid recollections of a few patients in whom with a large drainage of bile through the tube in the common duct there has been an increasing jaundice and death within a week. The death is apparently due to a terminal pneumonia but this I feel is coincidental rather than causal. In one such patient I had the assistance of Dr. Rabinowitch in determining that the 500 to 800 c.c. per day of drained bile contained a much less concentration of bilirubin (van den Bergh test) than did the blood. Autopsy revealed a shrunken liver, and the microscopic sections demonstrated columns of liver cells actually ruptured and

disintegrated. Such a condition is comparable with that of oedema of the lung following too rapid aspiration of a gross pleural effusion, or to anuria following the catheterization of a distended urinary bladder.

There is as yet no effective means of preventing this disaster. To remove a stone from the common duct it is necessary to open the duct, and immediately the dammed-up bile escapes in quantity. I see no way of adopting a technique of gradual reduction of pressure, as is used in the distended urinary bladder, except the gradual withdrawal of the bile by means of needle and syringe after exposure of the duct and prior to its incision.

To attempt in detail to outline the operative procedures which may be demanded under the protean conditions which may present in patients with obstructive jaundice is beyond the scope of this or any single presentation. I will therefore summarize.

Fortunately, in at least one-half the obstruction is benign; usually stone, occasionally benign papilloma, sometimes stricture. There is no such thing as "normal" anatomy of the bile ducts and vascular supply. What is described as normal is present in about 30 per cent, and no other group of "anomalous" distribution has more than 6 to 8 per cent. Therefore dissect cleanly and carefully, and be prepared to find a right hepatic duct emptying into the cystic duct or even into the gall bladder, the cystic duct blending with the common duct but not opening into it until perhaps near or at the ampulla, and, most important of all, the portal vein being in a plane anterior rather than posterior to the common duct. In fact, make it a rule when dissecting to uncover a common duct, to use a fine needle and syringe to aspirate the content of what looks like and should be from its position a distended common duct but may prove to be the portal vein.

Fortunate is the surgeon who is first on the field in operating for stone in the common duct. The presence of even a contracted deformed gall bladder is a guide through the mass of adhesions which may be present. Much too frequently a cholecystectomy is performed only to find later that floating "silent" stones were present in the common duct.

I desire to reiterate the oft-expressed opinion that palpation of the common duct frequently fails to reveal stones that are present; that indications for opening and thoroughly exploring the common duct are (1) the presence of small stones or bile sand in the gall bladder; (2) any thickening or dilatation of the extra-hepatic bile passages; (3) any evidence, either by pre-operative tests or by inspection, of recent or remote hepatitis; (4) any evidence, by pre-operative tests or by palpation of dysfunction or structural alteration of the pancreas.

The common duct having been incised, curved stone forceps are gently passed to grasp the stones, special care being taken to clean out the ampulla. The papilla of Vater should be well dilated by the passage of graduated sounds. With a soft rubber catheter the duct system is cleansed with normal saline under some slight pressure. And then, trust in a kind Providence that there are no stones out of reach in the intrahepatic ducts which later descend and give rise to a repetition of common-duct obstruction.

Closure and drainage of the common duct.—Immediate closure of the duct is undesirable for many reasons. It may leak; the trauma to the wall of the duct in removing an impacted stone may cause swelling with block to the flow of bile; free intrahepatic drainage is beneficial in overcoming the concomitant hepatitis and cholangitis. Therefore drainage of the duct is instituted.

This may be accomplished in different ways, *viz.*, a straight tube tied into a longish stump of the cystic duct with reinforced suture of the incision in the common duct. But there may be no cystic duct, the gall bladder having been removed at a previous operation. Or the cystic duct may be so contracted that drainage through it is not free. My own preference is to slit the cystic duct along into the common duct. This ensures that no small stones are imbedded in the mucous folds of the valve of Heister. Then to insert the largest size possible of a T tube, and suture the wall of the common duct incision closely about it. This reconstructs the common duct in a normal tubular shape, permits the bile to pass into the intestine, and is easily removed if a V has been cut out of the cross

arm opposite the junction of the upright of the T. A third method, mentioned only to be condemned, is the use of a straight tube passed through the incision in the common duct up and into the hepatic duct. This causes flattening and distortion of the common duct and encourages the formation of stricture.

Duration of drainage.—With little or no evidence of gross dilatation of the intrahepatic ducts and cholangitis, with thorough dilatation of the papilla of Vater, with bile flowing freely into the intestine through the T tube, with the bile draining to the outside of a clear bright yellow and free from muddy sediment, the tube may be removed in from 8 to 10 days. With the opposite conditions obtaining in whole or in part, drainage should be maintained for an indefinite period, and, in addition, repeated irrigations with warm normal saline solution should be employed with care. By this means bile mud and sand, and even small calculi, will be dislodged from the intrahepatic ducts, cholangitis will clear up, and a permanent satisfactory result will be obtained.

Occasionally one meets with a surprise in finding a fistula between the thickened contracted gall bladder and the duodenum, and the common duct filled with a mass of conglomerate stone. Removal of the stone and debris may reveal not the slightest sign of a lumen entering the duodenum. Drainage is instituted, and fortunately, after some weeks, the bile appears in the intestine and the biliary cutaneous fistula closes.

Stricture of the common duct.—Time does not permit the discussion of all the etiological factors producing stricture. Suffice it to say that unnecessary trauma, incomplete peritonealization of raw surfaces, and the unwise employment of drains in the operation of cholecystectomy may be responsible for a considerable proportion of the strictures. Stricture rarely produces a complete obstruction. For this reason the blood coagulation time is seldom very much delayed. But inasmuch as the relief of the stricture may require not only considerable dissection but also incision of the vascular duodenal wall in the formation of a plastic flap, it may be wise to be content to establish a biliary cutaneous fistula as a "first stage" to relieve

all jaundice. The operative procedure required to deal with the various sites and types of stricture may tax to the utmost the mechanical genius of the surgeon, and no attempt here will be made to describe details.

Malignant obstruction.—The obstruction may be at or near the ampulla as in carcinoma of the duct at this point, or carcinoma of the head of the pancreas. Attempt may be made to remove the disease radically as by the resection designed and carried out by Dr. Allen Whipple. Obstruction may be from metastatic glands in the gastro-hepatic omentum secondary to gastric carcinoma, etc.

If the obstruction is below the level of the cystic duct the gall bladder may be utilized to detour the bile into the stomach or duodenum by a cholecyst-gastrostomy or a cholecyst-duodenostomy. This is a very satisfactory palliation, provided the patient does not die of hæmorrhage. To more completely control oozing from the incised vascular mucous membrane of the viscera to be joined by anastomosis it is my custom to use a small Murphy button rather than suture.

In order to approximate the viscera without tension the gall bladder may require separation from its sulcus on the liver. Cholecyst-colostomy should not be done, as it is invariably followed by an ascending infective cholangitis. If the malignant obstruction is proximal to the cystic duct there may remain no choice but to establish a biliary cutaneous fistula. This is of value only when the itching is intolerable.

Adeno-carcinoma in the bile ducts may occur at various sites. It may be primary or be secondary to benign papilloma. If the obstruction is situated distal to the junction of the hepatic ducts the stools are acholic. But if either the right or left hepatic duct only is involved the picture is confusing, as there are signs of obstructive jaundice, but with a free flow of bile into the intestine.

Finally, in patients with obstructive jaundice, especially of long standing, there is frequently an insurmountable difficulty in diagnosis. It is not only justifiable but imperative that exploratory laparotomy should be done, as there are even chances that the obstructing cause is not malignant and is amenable to relief.

THE IMPORTANCE OF EARLIER OPERATION IN CHRONIC GALL-BLADDER DISEASE*

BY O. W. NIEMEIER

Hamilton

THE observations and conclusions upon this subject are based upon a study of a series of 529 operations upon the biliary tract at the Hamilton General Hospital, and also upon an analysis of a series of 143 cases operated upon by the author personally. No attempt will be made to give an exhaustive analysis of these cases, but simply to present those facts which have a bearing upon the phase of the subject under consideration. These series with the mortality rate are given below in Table I together with several others for the purpose of comparison.

TABLE I.

Series	Cases	Deaths	Percentage
Hamilton General Hospital	529	25	4.7
Niemeier.....	143	5	3.4
Glenn.....	360	12	3.3
Walters.....	1,011	29	2.8
Heuer.....	36,623	2,453	6.6
Fowler.....	1,296	71	5.9

The frequency of gall-bladder disease is a sufficient justification for presenting this subject for your consideration. Autopsy findings by various observers show that gall stones are found post mortem in from 20 to 30 per cent of all adults. Graham, Cole, Coopher and Moore, in their textbook on gall-bladder surgery, state that 20 to 25 per cent of all adults have gall stones and probably an equal number have cholecystitis without stones. Thus approximately 40 per cent of all adults have disease of the biliary tract. Moreover the disease is known to occur more frequently during middle life, and in our series the three decades from 30 to 60 years included approximately 70 per cent of our cases, (see Table II).

Estimation of the mortality rate in each age group showed a progressive rise in each decade. This is shown in Table III.

TABLE II.

Decade	Hamilton General Hospital series	Personal series
10 - 20	2	1
20 - 30	67	17
30 - 40	134	34
40 - 50	126	35
50 - 60	116	32
60 - 70	68	13
70 - 80	18	2

TABLE III.

Decade	Number of cases	Number of deaths	Percentage
20 - 30	67	3	4.4
30 - 40	134	1	0.7
40 - 50	126	7	5.5
50 - 60	116	7	6.0
60 - 70	68	5	7.3
70 - 80	18	2	11.1

While this rise is undoubtedly due in part to advancing age, it is probable that the more advanced stage of the disease is also a factor. As 76 per cent of the common duct cases were over 40 years of age, 54 per cent over 50, and 28 per cent over 60 years, we see that the later and more serious complications occur more frequently in the older age groups.

This is shown in Table IV in regard to stones and common duct lesions.

TABLE IV.

Decade	Percentage with stones	Percentage with common duct lesions
20 - 30	39	2.9
30 - 40	59	8.9
40 - 50	65	11.1
50 - 60	77	14.6
60 - 70	80	20.0

Operative and pathological findings also suggest a long duration of the disease in these older patients. That many of these patients could have been operated upon earlier with a lower mortality is indicated by the fact that in a considerable number of them the history extended back over a long period of years.

* Read before the Academy of Medicine, Toronto, April 6, 1937.

It is possible that certain chronic gall-bladder conditions may remain apparently latent for long periods of time. However, it is improbable that many of these conditions are symptomless, even though the patient may carry his gall stones to the grave. From clinical experience we know that these patients will endure considerable distress from digestive disturbance and suffer discomfort and even attacks of pain for long periods of time without seeking surgical relief. This fact is corroborated by a study of the histories of our cases. While many were indefinite as to the exact duration of symptoms there were frequent expressions such as "a long time", "many years", "considerable period", etc., in this connection. An analysis of 100 cases in which the duration of symptoms was definitely stated is shown in Table V.

TABLE V.
DURATION OF SYMPTOMS IN 100 CASES

Duration	Number of cases and percentage
Under 1 year	7
1 - 4	43
5 - 9	23
10 - 14	16
15 - 19	7
20 -	4
	50%

Thus 50 per cent of these cases had a history of five years or over; and 27 per cent of 10 years or more.

Examination of the histories also revealed that the vast majority of patients came for operation only after pain became intolerable, or when some serious complication such as jaundice developed. Table VI shows an analysis of the 143 personal cases from this standpoint.

TABLE VI.
AUTHOR'S SERIES OF 143 CASES

Complaint	Number of cases	Percentage
Biliary colic.....	50	34.9
Acute cholecystitis...	28	19.5
Jaundice.....	21	14.6
	99	69.0

Thus we see that 99 patients, or 69 per cent, postponed operation until they were driven to it by unbearable pain or some acute emergency or serious complication. This tendency to procrastinate in seeking surgical treatment on

the part of the patient is partly due to the dread of surgery and also to the fact that periods of quiescence or apparent latency are often present during the course of the disease. During these intervals, when the only symptoms may be digestive disturbance, the patient as well as the physician is lulled into a false sense of security. One of our patients had had only slight symptoms following several attacks 18 years previously, until he developed the attack which brought him to us with an acute free perforation of the gall bladder. As most of these patients had been under the care of physicians from time to time, and the diagnosis of gall-bladder disease had been made in the majority, it is apparent that the tendency of the patient to delay is but a reflection of the attitude of physician towards these chronic lesions of the gall bladder. Many physicians believe that chronic latent gall-bladder disease is a harmless condition, for which surgery is not indicated unless some acute manifestation or alarming complication develops.

That this attitude of *laissez faire* is not in the interests of the patient I believe is evident from our study. An analysis of the hospital series of cases shows that there is a progressive rise in the mortality rate with the advance in the pathological process present. In Table VII these cases are classified with reference to the type of lesion present and the mortality in each group.

TABLE VII.
529 CASES: HAMILTON GENERAL HOSPITAL

Lesion	Number of cases	Deaths	Percentage
Chronic cholecystitis without stones.....	155	3	1.9
Chronic cholecystitis with stones.....	304	12	3.9
Acute cholecystitis.....	70	10	14.3
Common duct cases.....	64	7	10.9

Chronic cholecystitis without stones we accept as the earliest and least advanced type of the disease, and in this condition we find the lowest mortality, 1.9 per cent. As gall stones, with the possible exception of the cholesterol stone, are regarded as being a secondary development in chronic cholecystitis, we classify the group with stones as a more advanced stage of the disease. Here we have a mortality of 3.9 per cent, double that in the

first group. As stones were present in 85 per cent of the cases of acute cholecystitis, the latter process is regarded as being a further stage and later complication chiefly affecting those patients who already have stones. Here the mortality rate rises abruptly to 14.3 per cent, showing the penalty which the patient must pay for deferring operation until this complication develops. Those cases with jaundice and other evidences of common duct involvement necessitating choledochotomy, it will be agreed belong to the later sequelæ of the disease. In this group the death rate was 10.9 per cent. These are significant facts, and in my opinion provide an argument for earlier operation in these patients before advanced disease and dangerous complications render their surgical treatment hazardous.

This rise in mortality rate with the advancement of the disease is not surprising. Every surgeon who deals with gall-bladder cases is frequently called upon to operate upon patients whose toxæmia, acute infection, or extreme jaundice renders them very precarious risks. He also encounters at operation such dense adhesions to other organs and such infiltration and induration of the structures in the hepato-duodenal ligament as to make operation a matter of great technical difficulty, as well as an extremely hazardous procedure. In three of our cases there were fistulous communications with other organs, two with the duodenum and one with the colon.

Too frequently one is compelled to be content with a drainage of the gall bladder in some of these very densely adherent cases, as well as in some of the very acute infections and in certain poor risk patients. The frequency with which the surgeon was forced to resort to cholecystostomy in our series is shown in accompanying Table VIII.

TABLE VIII.
CASES OF CHOLECYSTOSTOMY

Series	Number of cases	Cholecystostomy	Percentage
Hamilton General Hospital.	529	92	17.3
Personal.....	143	15	10.4

As it is generally accepted that the infection resides principally in the wall of the gall bladder, it is obvious that if we are to eradicate the focus of infection we must remove the

gall bladder. As this was considered inadvisable or unsafe in 17 per cent of our series it is also obvious that operation at an earlier stage of the disease would be desirable when removal is not only possible but attended by a low mortality. Surely any system of management of these cases which leaves the patient with his focus of infection in from 10 to 17 per cent of cases is far from being ideal.

The prevalent policy of delay in the surgical treatment of chronic gall-bladder disease also results in damage to adjacent organs such as the liver and pancreas. Liver damage or hepatitis can frequently be seen in the gross, and is often visibly more marked in the immediate vicinity of the gall bladder. While some workers claim that cholecystitis is secondary to hepatitis as regards its etiology, there can be no doubt that when gall-bladder disease has become established, and especially if there are recurrent subacute exacerbations, progressive damage to the liver is almost certain to occur. The free lymphatic communication between the liver and gall bladder makes this almost inevitable. McCarty reports hepatitis present in 81 per cent of patients with chronic gall bladder disease, and Graham records its presence in 87 per cent. Routine palpation of the pancreas will also often reveal a thickened hardened gland in the cases of long duration. When we remember the rôle which gall-bladder disease is believed to play in acute pancreatitis and the high mortality of this condition we have another argument for its earlier eradication. Once these destructive changes have occurred in adjacent organs, the patient, even after cholecystectomy, will be left with permanent damage. This may account for the failure of cholecystectomy to completely relieve the symptoms in certain late cases. We must also remember that carcinoma of the gall bladder occurs in a small percentage of cases. As gall stones are present in from 80 to 90 per cent of all cases of carcinoma of the gall bladder they are believed to be an important etiological factor. The incidence of carcinoma was only 0.37 per cent in the hospital series of 529 cases.

In addition to these local effects of neglected chronic gall-bladder disease there are other insidious and more widespread effects. Many patients with apparently latent lesions pay the penalty of delay in the form of damage to

distant organs. A considerable literature has accumulated regarding the diseased gall bladder as an etiological or aggravating factor in systemic disease. As a focus of infection it is regarded by many as ranking in importance next to teeth, tonsils and sinuses. A number of cases illustrative of this less obvious rôle were met with in the personal series, and several of these will be briefly described.

There were three cases of arthritis of long standing which showed marked improvement following the removal of a diseased gall bladder.

One of these patients who had been bed-ridden for over a year developed attacks of biliary colic of such frequency and severity that she demanded operation. Somewhat to our surprise this patient was up and walking about the ward before leaving the hospital, and is now able to do most of her own housework. The other two were less severe cases of arthritis, but both have been relieved of their symptoms following cholecystectomy.

These findings are in accordance with those of Graham, Cole, Cooper and Moore who make the following statement "We have known cases of chronic arthritis relieved by cholecystectomy after the presence of gall-bladder disease was established". Thus in the absence of other foci of infection it would appear logical to investigate the gall bladder more frequently in our arthritic patients, and where it is found diseased to seriously consider its removal.

We have also met with two interesting cases where the diseased gall bladder appeared to be an important factor in associated cardiac disease.

One patient, a female, 55 years of age, with præcordial pain, dyspnoea and attacks of fibrillation with weak rapid pulse was also suffering from repeated attacks of biliary colic with slight jaundice. A non-functioning gall bladder was demonstrated by cholecystography and electrocardiographic changes indicative of organic cardiac disease were shown on two occasions. On the advice of the internist operation was considered, but cancelled twice because of an exacerbation in the cardiac condition. Finally, after the lapse of several months, pain had become so continuous and jaundice so intense that it was decided to take the risk of operation. We performed a speedy cholecystectomy and exploration of the common duct, and the patient had an uneventful convalescence and made a good recovery. Her cardiac symptoms, including the electrocardiographic changes, entirely disappeared in a few months, and she is now perfectly well and doing her own housework.

Another, more elderly, patient with myocardial damage and electrocardiographic changes was transferred from the medical service for cholecystectomy as she had a chronic gall-bladder infection which was causing frequent attacks of pain. After careful preparation cholecystectomy was carried out and followed by marked improvement, but not by complete disappearance of the cardiac symptoms.

One wonders whether earlier operation might have been followed by more complete relief in this case.

Time will not permit elaboration of the numerous references in the literature, but recently Fitz Hugh and Wolferth have reported 6 cases in which cardiac disease with definite electrocardiographic changes improved or disappeared following cholecystectomy. Mayo, Babcock and others have called attention to the etiological relationship of gall-bladder to cardiac disease, and Schwartz and Herman and Willius have pointed out the frequency with which the two conditions are associated. We must of course bear in mind the fact that both conditions are commoner after middle life.

An important aspect of this relationship of gall-bladder and cardiac disease is its possible bearing upon the mortality following gall-bladder operations. It is possible that some of the unexpected deaths following gall-bladder disease are due to unsuspected and untreated co-existing cardiac conditions. It is needless to state that the closest cooperation between the internist and the surgeon is essential in the treatment of these cases.

There were two diabetic patients who showed gratifying improvement following the removal of a diseased gall bladder.

One of these an elderly woman had been requiring 60 to 70 units of insulin a day and had such marked digestive disturbance that she could not be properly dieted. Following operation she was able to eat normally and required only 10 to 15 units twice a day.

Another patient who had been getting 40 to 50 units of insulin a day was satisfactorily controlled by diet alone following the removal of a thick-walled gall bladder containing stones.

The beneficial effect in these cases is probably due to the removal of the focus of infection and the relief of the digestive disturbances rather than to any direct effect upon the pancreas. Cholecystectomy in these diabetics would appear to be particularly indicated where marked digestive disturbance interferes with the proper dietetic treatment of the patient.

Thus statistical, pathological and clinical evidence all emphasize the importance of earlier surgical treatment of chronic gall-bladder disease. This of course demands earlier recognition of the condition. With modern diagnostic methods this should present little difficulty. Cholecystography will demonstrate disease of the gall bladder as well as variations in its func-

tion with almost mathematical accuracy in from 95 to 98 per cent of cases. This very ease of diagnosis may lead us to neglect other methods of examination, such as a careful history and general physical examination. Having demonstrated the trouble in the gall bladder we may overlook other and even more important lesions from which the patient may be suffering, and which may be the actual cause of the symptoms.

Regarding the advisability of the removal of the non-functioning gall bladder and the gall bladder containing stones in patients having pain or marked dyspepsia there is general agreement. There is a greater tendency to procrastinate in these cases when symptoms are slight and when attacks of pain only occur at comparatively long intervals. Personally, I believe that all of these non-functioning gall bladders, with or without stones, but particularly if stones are present, should be removed. Even though apparently latent they may be acting as foci of infection or sources of toxæmia. Moreover, there is the menace of an exacerbation of acute cholecystitis or such sequelæ as common duct stone, jaundice, or cholangitis.

In connection with the gall bladder showing the slighter degrees of involvement and without stones there may be some difference of opinion regarding treatment. Graham and others have reported that their results following cholecystectomy have been attended by a lower percentage of relief of symptoms than in those cases where stones were present. Personally, I believe this to be due in many instances to errors of diagnosis.

Other lesions are frequently associated with gall-bladder disease and may easily be overlooked. Wilkie has pointed out how closely duodenal ulcer in women resembles gall-bladder disease in its clinical manifestations.

In our series duodenal ulcer and chronic appendicitis were found in association with gall bladder disease as shown in Table IX.

TABLE IX.
HAMILTON GENERAL HOSPITAL SERIES

Cases	Duodenal ulcer	Percentage	Chronic appendicitis	Percentage
529	6	1.1	118	22
143	4	2.7	26	18

Great care must be exercised in the investigation of those cases having minimal changes, by rigid pre-operative examination, including a careful history, physical examination, with a gastro-intestinal x-ray as a routine. If all other lesions can be reasonably excluded and these cases are to be submitted to surgery one should carry out a most careful exploratory examination at the time of operation. Most of the unsatisfactory results in this group are I believe due to the overlooking of some associated lesion which is causing the patient's symptoms. One such case in my personal series with cholecystographic evidence of diminished gall-bladder function had a cholecystectomy with very slight relief. Further investigation revealed an infected hydronephrotic right kidney and the patient was completely cured by nephrectomy.

There can be no objection to giving these milder cases a trial of medical treatment, by diet, removal of foci of infection and repeated duodenal drainage as advised by Rehfuß. But if symptoms persist after a reasonable trial and all other lesions can be excluded, operation should be carried out. We have no reason to be disappointed in our results in such cases. Surely this is the ideal stage at which to eradicate the disease, as the mortality is lower and permanent damage to other organs is comparatively slight.

SUMMARY

1. Earlier operation in chronic disease of the gall bladder is indicated to lower the mortality and to prevent irremediable damage to other organs.
2. A diseased gall bladder, even though apparently quiescent, is a menace to the patient because of the possibility of the development of an attack of acute cholecystitis or some other serious complications, such as common duct obstruction with jaundice, liver damage, or cholangitis.
3. The diseased gall bladder should also be remembered as a possible etiological or aggravating factor in systemic disease.

I wish to acknowledge my indebtedness to Dr. R. E. Nicholson for his assistance in the examination of the charts and obtaining the statistical data in these cases.

ENDOCRINE FACTORS IN NORMAL AND ABNORMAL MENSTRUATION*

BY MELVILLE C. WATSON, M.B.

Toronto

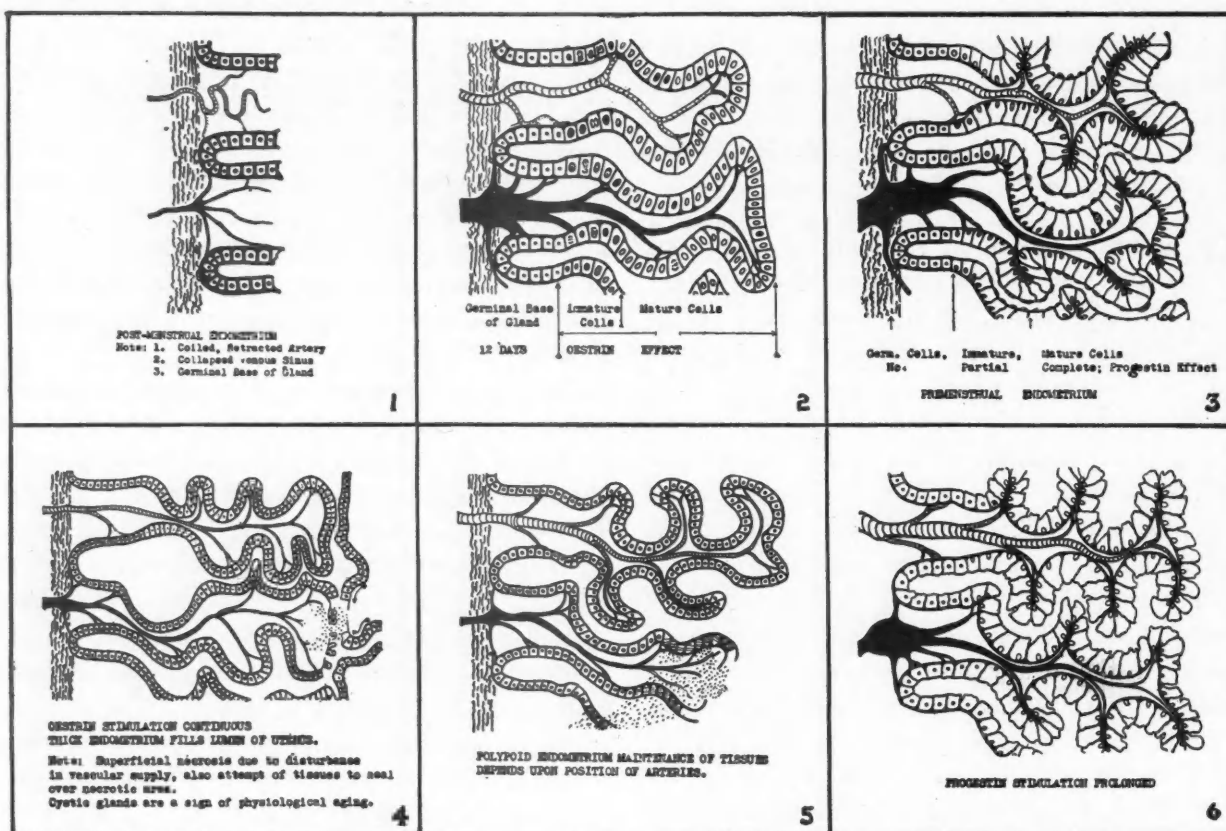
AN accurate record of the date of onset and the duration of the menstrual flow and the proper interpretation of that record are of the first importance in the differential diagnosis and the treatment of all diseases which affect the uterus, the Fallopian tubes and the ovaries. Normal menstruation is an index of normal ovarian function. Therefore the clinician must recognize the difference between a menstrual flow which represents normal menstruation and a menstrual flow which represents abnormal menstruation. There is only one sequence of events in the ovary and endometrium which results in normal menstruation, and free blood in a uterine discharge apart from this physiological sequence should more properly be known by the simple but adequately descriptive title of "uterine bleeding".

It is the purpose of this paper to describe the tissue changes in the endometrium during a normal menstrual cycle, and to compare the normal endometrium with abnormal conditions which result from continued oestrin or continued progestin secretion by diseased ovaries. For the sake of brevity and simplicity I have represented in six diagrammatic sketches the results of observations made on many hundreds of sections from the endometrium. Each sketch will show two or more points in connection with hormone action and the resulting tissue changes. The migration of white blood cells and the tissue changes in the supporting stroma have been disregarded in this discussion. This is because all these tissues react in a similar manner toward the accomplishment of a similar purpose—the maintenance of vitality in a fertilized ovum, and the consideration of the epithelial tissues will serve as an index in a study of the whole endometrium.

It is important to emphasize the fact that the endometrium previous to the dissolution which results in a normal menstrual flow seldom exceeds a depth of 3 or 4 mm. from the uterine

lumen to the muscle layer. It is also important to emphasize that every endometrial gland, regardless of how it may appear in microscopic section, extends from the germinal portion of its base near the muscle of the uterus to a gland orifice, either singly or in conjunction with other glands on the surface of the endometrium. It has been definitely established that the growth of these glands, which is a result of cell division in their epithelial lining, is controlled by a hormone produced by the developing Graafian follicle, and having a chemical formula which is basically similar to oestrone. The apparent increase in the number of glands in a section taken during the growing or proliferative phase is due entirely to an increased tortuosity of the originally existing glands whereby each gland is cut across at many intervals in the one section. Fig. 1 shows the basal portion of three glands in a diagrammatic longitudinal section immediately after a major tissue loss at the time of normal menstruation has occurred. The free end of the arteriole is thrombosed, and automatic retraction is represented by the coiled appearance of the arteriole, two conditions which prevent further bleeding from the arterial side of the vascular bed. The venous sinus at the gland base is collapsed because, due to the disruption of the vascular bed, practically no blood returns in the remaining portion of the afferent venules. Some venous blood may be regurgitated through these broken venules as the uterus contracts. Fig. 2 illustrates the active growth which occurs in the germinal cells at the base of the gland under the influence of oestrin. The basal portion of the same three glands, drawn to the same scale as Fig. 1, is shown. Each gland is divided into three areas in accordance with observations that we have made. The germinal base is unchanged; immediately above, in the second area, active growth is indicated by mitotic division in the nucleus of the dividing cells. It has been observed that these growing epithelial cells are matured by oestrin as they reach the upper portion of the gland and the surface epithelium,

* Read at the Sixty-eighth Annual Meeting, Canadian Medical Association, Section of Obstetrics and Gynaecology, Ottawa, June 23, 1937.



and that cell division is not a common finding in the surface epithelium or the upper portion of the gland after the fourteenth to eighteenth day of the normal cycle. The vascular bed is shown to have responded to the growth stimulus by the lengthened artery and vein and the fact that the venous sinus is now distended by a return flow of venous blood. In connection with the changes which occur in the endometrium previous to a normal menstrual flow it has been further definitely established that a hormone, progesterin, from the corpus luteum body, is responsible for the conversion of these matured epithelial cells into active functioning or secreting cells. This hormone, progesterin, has a formula which is identical with a synthetically produced substance known as progesterone. In the course of our experimental work we have observed that the main effect of progesterin or progesterone is exerted on those epithelial cells which have been matured by oestrin. The immature epithelial cells near the base of the gland are not affected by progesterin. Fig. 3 is a diagrammatic sketch illustrating a section of premenstrual endometrium. The basal portion of the gland is shown as it appears in Figs. 1 and 2, unaffected by progesterin stimulation. The immature cells immediately above the base are

shown to be partially affected, while the mature cells near the surface show the full effect of progesterin. The nuclei are at the basement membrane, there is a definite cytoplasmic increase in the cell, and the cell membrane bulges into the lumen of the gland. The glands are coiled and looped, due to the increase in the size of the individual cells, and the vessels are packed within the loops, where the stroma is now deficient because it has been literally crowded out.

Quite recently we have obtained some experimental evidence to justify a conclusion that the tissue loss during normal menstruation is limited to those mature cells in the glandular and surface epithelium which have been completely matured by oestrin and fully activated by progesterin. This conclusion was based on the observation that the internal economy of these cells was so altered by the accumulation of the secretion within the cell membrane that the cells could not return to their former state after the progesterin stimulus was withdrawn. Accordingly, dissolution and death results if the progesterin is discontinued. As the immature cells in the germinal portion of the gland base are not affected by progesterin they are not involved in the loss of tissue, and they remain to regenerate under the influence of oestrin.

Fig. 4 is a diagrammatic illustration of the endometrium when it has been maintained under the continuous influence of œstrin for a indefinite period of time. Tissue growth is continuous in this type of endometrium, and tissue loss is limited to areas of superficial necrosis. In the absence of disease, which is frequently local in such an endometrium, the degree of tissue growth depends entirely on the extent to which the tissues are stimulated by œstrin. Consequently the microscopic picture may resemble the normal early or late proliferative phase. The effect of a continuous growth stimulus from œstrin over a long period of time is eventually the complete filling of the uterine lumen with endometrium in the proliferative phase showing many signs of ageing, amongst which cystic dilatation of the glands is prominent.

The condition shown in Fig. 4 persists under any set of circumstances which interferes with the normal ovarian cycle in a way which causes arrest of follicular development and a resulting continuous secretion of œstrin. It is perhaps most commonly found during the menopause and in early adolescence, but it frequently intervenes in the reproductive era of an apparently normal patient. The factors which interfere with the ovarian cycle and so give rise to this condition can be grouped for the sake of brevity under three main headings. First: the endocrine factor, which is primarily due to a disturbance in the pituitary ovarian relationship, similar to that which occurs normally at the menopause. From personal experience the influence of hyper- or hypo-thyroidism on the pituitary-ovarian linkage is negligible except in extreme cases of hypo-thyroidism where all tissues are affected by a lack of oxidation in their nutritive supply. It must, however, be remembered that variations in thyroid function are commonly found in association with endocrine disturbances that also affect the ovary. Second: inflammatory processes in the ovary. Third: new growths in the ovary which involve the endocrine producing elements, *e.g.*, granulosa cell tumours. Absence of corpus luteum formation is a constant finding. The patient suffers from amenorrhœa because the ovarian cycle is not complete and there is no macroscopic loss of tissue from the endometrium. The symptoms are, therefore, total amenorrhœa, in which case there is no bleeding of any kind, or amenorrhœa masked by slight fairly regular or irregular

bleeding, by fairly profuse regular or irregular bleeding, or by continuous uterine bleeding. The stroma is usually found to be infiltrated with free red blood cells in many areas, even apart from those occasions when free red blood escapes into the lumen of the uterus. In many cases the actual bleeding can be explained as due to a superficial necrosis which results from the disturbance in vascular supply, which in turn is caused by trauma from pressure in the uterine lumen or by an inflammatory process. In other instances the bleeding appears to be caused by an alteration in œstrin concentration. While we know that a sudden alteration in œstrin concentration will cause actual bleeding from this type of endometrium in the human being, the exact mechanism by which it is produced is not clearly understood.

Apart from the fact that uterine bleeding from an endometrium of the type shown in Fig. 4 is indicative of a disturbance in ovarian function that calls for an extensive clinical investigation, it is also important for the gynæcologist to recognize the condition because of the possibility of disease in the endometrium itself. In my opinion this type of endometrium is the nidus for infections which result in chronic endometritis, and as a result of the continuous attempt of the tissues to heal over necrotic areas on the one hand and the chronic irritation with tissue necrosis on the other (Fig. 4) the formation of endometrial polypi (Fig. 5), endometriosis, and the tendency to a malignant type of growth is strongly favoured.

The symptom, uterine bleeding, is also commonly produced by a condition where the endometrium is maintained in the functional phase by the continued secretion of progestin. For reasons as yet unknown to us the corpus luteum frequently remains in the ovary either as a cystic tumour or in an abnormal solid form. Progestin is continuously secreted by many of these tumours and as a result the endometrium is maintained in the functional or pre-menstrual phase (Fig. 6). The microscopic picture differs from the normal pre-menstrual endometrium in many respects; the epithelial cells become exhausted, as is shown by the irregular outline in Fig. 6, and superficial necrosis with chronic inflammation and free bleeding from the vascular bed is the rule. Healing occurs less readily in an endometrium which is maintained by progestin than it does where œstrin is the stimulat-

ing hormone, hence the bleeding period is liable to be prolonged or continuous. The condition is most commonly found late in the reproductive era of women who have had multiple pregnancies.

The development in the endometrium which precedes a normal menstrual period and the type of endometrium which is typical of prolonged oestrin or prolonged progestin effect have been briefly described. The importance of a differential diagnosis between these three conditions has been stressed. In an attempt to make such a diagnosis one must further stress (a) accuracy in recording symptoms, combined with keen clinical observation; (b) histological examination of endometrial tissue; and (c) chemical estimation of the secretion products of ovarian hormones in the urine.

To the practising physician the importance of a careful physical examination in the light of information obtained from an accurate history can never be over-estimated. It will take some time to accurately appraise the general metabolic effects which are produced by oestrogenic substances, but those who have had some experience with research work along this line are already aware of the fact that the water balance and the capillary blood flow appear to respond to the influence of oestrin. It is my impression that the rise in oestrin concentration previous to a normal menstrual period causes an increase in water retention and an increase in blood volume which is reflected in the patient by an increase in tissue turgescence, particularly in the breasts, which is apparent on repeated examinations. The sudden decrease in oestrin concentration which occurs immediately previous to and during the menstrual flow appears to result in a temporary dehydration, lowered blood volume, and a resulting decrease in tissue turgescence. If the fluid intake of the patient has been adequate throughout the cycle these symptoms always accompany normal menstruation. They are absent in the cases of simple uterine bleeding. In the thin, dehydrated,

anaemic patient who suffers from uterine bleeding no changes can be detected. The plethoric, obese patient who bleeds in the absence of an ovarian cycle remains permanently "stuffed" and complains of that feeling. This latter type of patient was formerly thought to have menstrual periods without evidence of general symptoms. These patients are unaware of the onset of uterine bleeding.

Histological examination of endometrial tissue is a most important diagnostic procedure. The pathologist in the future should advise the clinician that the section is from a normal proliferative or functional phase previous to menstruation, or that it is from an endometrium which is maintained in either the oestrin or progestin phase, and he should state approximately the length of time it has been so maintained. It is, however, unfair to ask the untrained pathologist for an accurate diagnosis without having supplied him with the essential facts from an accurate history of the menstrual flow.

Venning and Browne have recently described a method for the quantitative determination of sodium pregnandiol-glucuronide in human urine. There appears to be a definite relationship between the excretion of this substance and the metabolism of the corpus luteum hormone, progestin. In several normal cases reported none of the pregnandiol complex was detected in the urine up to the time of ovulation; after the estimated time of ovulation the substance appeared in the urine and was excreted continuously for ten days, disappearing two and one-half days after normal menstruation began. At this early date the development of this test appears to be a great advance in the effort to determine the presence or absence of functioning luteal tissue. More accurate diagnosis of the conditions which cause uterine bleeding will eventually lead to a more desirable and effective form of treatment than many patients are receiving at the present time.

CORPUS LUTEUM HORMONE.—K. Ehrhardt and E. Hardt have investigated human and animal placentae for the presence of corpus luteum hormone, and have come to the following conclusions. The hormone is present in human placenta between the fifth and the eighth months of pregnancy. It was found in two out of six cases in extracts of horse placenta, and in all cases of goat placenta, but was absent in cow, sheep,

and dog placenta. Its presence could not be demonstrated in the fetal organs, but slight traces were found in the fetal urine. A large quantity was found in an extract of a hydatid mole. The administration of this hormone to pregnant mice caused intra-uterine death of the fetuses. It should, therefore, not be given indiscriminately to pregnant women.—*Med. Welt*, May 29, 1937, p. 745. Abs. in *Brit. M. J.*

FEVER THERAPY

BY E. E. SHEPLEY, M.D.

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FROM many dependable sources there is now available a wealth of literature relating to fever therapy and its value in certain pathological conditions which have not responded satisfactorily to the time-honoured methods of treatment. It is the purpose of this article to review briefly the present status of this particular type of therapy, and to refer specifically to certain conditions in which it has proved not only its very great utility but also its remarkable versatility.

It is admitted that the writer's practical experience in this field is restricted to 250 actual treatments given in the department of physical medicine in the Saskatoon City Hospital. Sixty patients have thus been treated. To Kimble, Neymann, Schmitt, and Osborne, of Chicago, we

this has proved most satisfactory. In this cabinet the patient lies on a thick rubber mattress in a roomy compartment and is entirely free from restriction. During treatment the patient's body is constantly surrounded by a humidified circulating current of heated air. The humidifier, the air current fan, the thermostatic temperature control, and the fresh cool air intake are all conveniently housed in the lower half of the cabinet. Control switches are located in the end of the cabinet through which the patient's head protrudes and near which the specially trained nurse-technician constantly stands. A large coil provides the electromagnetic field which is responsible for the induction of temperature, and this is located in the top of the cabinet, near to, but never in actual contact with, the patient's chest wall (Fig. 1).

PROCEDURE

Little preliminary treatment is given, but careful selection is all important. The patient reports at the department at 8.00 a.m., having already had a light breakfast. Thirty grains of bromides by mouth, or one grain of luminal (hypodermically), are given at once. One-quarter to one-half an hour later the patient strips completely and enters the cabinet, and is given 4 g. of table salt in a rather concentrated solution. In the brief waiting period it is an important duty of the attending nurse to secure the patient's entire confidence.

During the treatment extra sedatives such as bromides or luminal may be given. Small doses of morphia are given in the restless apprehensive types. Liquids are freely given throughout the treatment. An ice-cold cloth applied on the forehead during the treatment and a fan near the head greatly contribute to the comfort of the patient. Rectal temperatures are taken at one-quarter hour intervals throughout the treatment. In case of emergency ice is always available to reduce an abnormally high temperature. This should practically never be required. During treatment it may be necessary to reduce the cabinet temperature, and this is provided

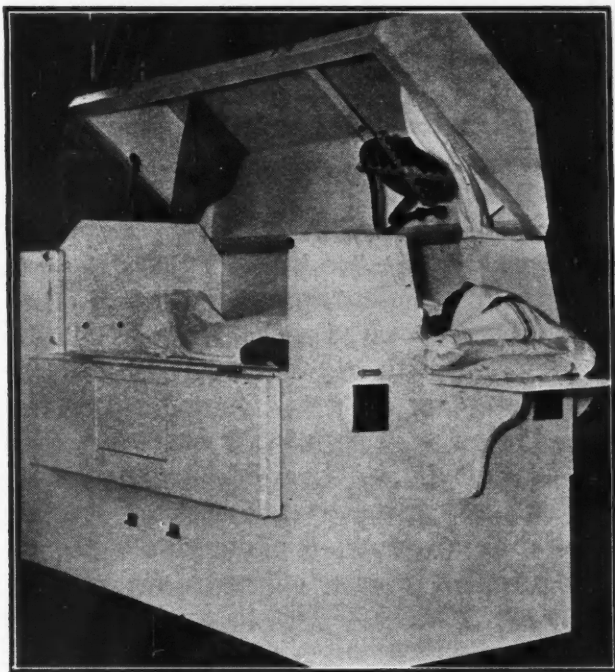


Fig. 1

are indebted for the opportunity, so very freely afforded, to study their methods, to see their actual cases, their case records and their most exhaustive research data.

In instituting this work the hospital's workshop, under the supervision of the hospital superintendent, undertook the construction of a modified Kimble type of therapeutic cabinet and

for by a fresh air intake valve. A thoroughly trained nurse-technician, ever tactful but always firm, is essential to successful fever therapy.

A typical chart of a fever treatment usually shows a definite sequence. In the accompanying chart, the patient (Miss B.V., 20, white, 5 feet, 100 lbs. Diagnosis: acute g.c. salpingitis) entered the cabinet at 8.15 a.m. At this time the pulse was 80, the respirations were 18, and the oral temperature was 98.2°. The in-

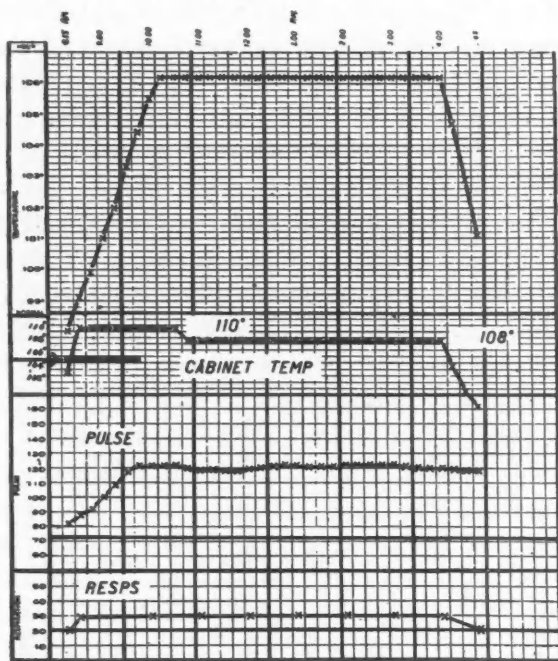


Fig. 2.—Fever therapy chart; inductotherm in operation from 8.15 to 9.45.

ductotherm was immediately set in operation and the humidified air surrounding the patient was gradually raised to 110°. A gradual rise in temperature, pulse and respirations is seen in the chart. At 10.15 a.m. the temperature reached 106°. The pulse was then 120 and the respirations were 28. The inductotherm, it should be noted, was turned off at 104°, two degrees below the predetermined temperature. When the patient's temperature reached 106° the cabinet temperature was gradually reduced to 108°, and this temperature was maintained until 4 p.m.; the inductotherm was not in use after 9.45 a.m. Once the temperature reaches the predetermined height it may be kept at this level simply by maintaining the cabinet temperature approximately two degrees above this level. In the present case the temperature of the cabinet was reduced to room temperature at 4.00 p.m. and the patient was removed at 5.00 p.m. The temperature at this time was 101°.

After the cabinet treatment is completed the patient is returned to bed in blankets. When the temperature has fallen to normal the patient is sponged and dried, is permitted to sleep as desired, and to get up later, at will.

TEMPERATURE PRODUCTION

The temperature of the human body may be readily raised above the normal physiological level in many ways. These methods fall into two groups, those in which heat is produced externally, and those in which heat is actually generated in the body tissues. In the former group are found the hot water bath, the steam bath, the electric cabinet bath, infra-red ray baths and the electric blanket; in the latter group are diathermy, inductothermy, non-specific protein therapy, and controlled inoculation with malaria. Since electrical energy is so commonly the source of heat, the production of fever by electrical means is sometimes spoken of as "electropyrrexia". On the whole, external heat appears unsuited to the production and maintenance of a prolonged fever, because it has been found to be too exhausting and to be by no means devoid of actual danger. Not only is this type of heat production non-physiological, but the danger of heat exhaustion is considerable.

In those institutions which have been most successful in placing fever therapy upon both a rational and practical basis artificial fever is obtained by the use of some form of penetrating heat, that is to say, by diathermy or inductothermy. In diathermy heat is produced in the tissues because of the resistance they offer to the passage of the high frequency current (+-2,000,000) as it traverses the tissues between large metal electrodes which are firmly applied to the skin on opposite sides of the patient's body. In inductothermy a much higher frequency (12-15,000,000) is employed. This current is passed through a large, single coil placed close to the patient, but with no direct skin contact. Thus enveloped in a high frequency electro-magnetic field there is induced in the tissues a current of similar high frequency, one of the effects of which is the production of heat. In that the heat production is within the body the method more closely approximates the normal physiological production of heat. Experimental work with the inductotherm¹ and saline solutions has shown that a

physiological saline solution (0.85 per cent) has the same electrical conductivity as blood plasma. The conductivity of such tissues as the skin, adipose tissue, and muscle is equivalent to that of saline solutions of lower concentrations. Since the blood plasma is more conductive than all other body tissues it is here that the greatest heat is produced. In diathermy the reverse obtains, and this explains the discomfort that patients sometimes experience in this form of treatment. Being much less conductive, the highest temperatures are found in the skin and fat, and quite unnecessary distress is thus often produced by the use of diathermy.

TEMPERATURE DISTRIBUTION IN THE BODY

McCallum² holds that "temperatures ranging from 100 to 103° are comparatively ineffective in combating infection and that there exists a definite relationship between the clinical course of a disease and the thermal death point of the causal organism." For example,³ *in vitro*, low temperatures produce no demonstrable effect upon the *S. pallida*, but a temperature of 104° for two hours will destroy the organism. A slightly lower temperature maintained for several hours almost certainly seriously depresses both the vitality and the reproductive capacity of the organism. *In vivo*, in electropyrexic treatment, in addition to the effect of heat upon invading organisms, the effect of high temperatures in mobilizing the body's defensive mechanisms is also to be considered.

Knowledge concerning the distribution of artificially produced temperatures in the body is of practical interest.⁴ Temperatures in the depth of tissues are about two degrees higher than in the overlying subcutaneous tissues. In the extremities in their distal portions subcutaneous temperatures are invariably two to three degrees less than those of similar tissues in the abdomen and thorax. At the height of temperature production the temperature of the spinal cord and the basal cistern is approximately one-half a degree less than that found in the rectum. In treatment by external heat the subcutaneous temperatures are very much higher than those found when inductothermy and diathermy are used. The most rapid production of artificial fever is secured by means of diathermy. In this method the patient is insulated against heat-loss by means of an enveloping bag or cabinet specially prepared

for this purpose. With suitable diathermy apparatus the desired temperature may be attained in approximately 1½ hours. With inductothermy a slightly longer period, approximately 1¾ hours, is required. When external heating measures are employed up to five hours may be required to secure an adequate temperature level.

THE BIOCHEMICAL REACTIONS INCIDENT TO FEVER THERAPY

The biochemical reactions incident to fever therapy necessarily become of practical interest.^{4, 5} In general it may be stated that the effects of fever therapy are similar to those of natural fever. McCallum has said, "Fever is a beneficial reaction in that the production of immune bodies proceeds best in the presence of temperatures, that fever processes become advantageous in that they are doubtlessly associated with the production of substances which combat injurious agencies that have invaded the body". The blood of treated patients constantly shows an increase of cells and Hgb. content. The polymorphonuclears are relatively increased. The blood chlorides, calcium, urea, non-protein nitrogen, and sugar are all increased. The uric acid content is not changed but creatinine shows an increase. This, in the main, is a picture of increased katabolism and blood concentration. Due to stimulation of the bone marrow, immature red cells are occasionally found. This stimulation suggests the possible application of fever therapy to the treatment of certain anæmias. No variation in the opsonic index, in the agglutinin or in the complement content has been noted. Ordinarily, the sedimentation rate normally corresponds to that clinical improvement which is registered in the case in question. The blood lactic acid shows no variation from normal. A loss of carbon dioxide from the blood is always found, and its combining power is markedly diminished. This corresponds with a slight pH shift to the alkaline side. In many patients the blood phosphorus may fall below normal limits. During treatment the blood pressure shows a systolic rise and a diastolic fall. After treatment the blood pressure is lowered and may remain low. The amount of lowering varies from 10 to 45 mm. of mercury. This is particularly noted where high tempera-

tures have been used in repeated treatments. A lowered non-protein and urea nitrogen is also found after treatment.

Where excessively high temperatures are administered over prolonged periods one may find evidence in the tissues of intense peripheral hyperæmia and occasionally focal hæmorrhages. Parenchymal cells may show cloudy swelling and fatty degeneration. Evidence of hyperplasia is not uncommon and depletion of glycogen may be noted. A maintained temperature of 105° produces no abnormal lesions.⁶ A microscopical study of the nail beds during treatment constantly reveals an enormous increase in both the size and number of visible capillaries, and the rate of flow is very greatly augmented. This becomes a practical index of the circulatory changes which obtain throughout the entire body during fever therapy. This spectacular change in the character of the local capillary circulation cannot but exert a most profound influence upon local metabolic processes, and it becomes evident that degenerative tissue changes must thereby be most definitely and effectively combated. These tissue reactions are identical with those which occur in malarial treatment and in the course of the more acute infectious diseases.

During a major fever treatment two to five pounds of sweat are lost, and 18 to 24 g. of sodium chloride excreted. The sweat, at first acid, later becomes neutral. Sweating, usually general in distribution, in certain cases may be more or less local in type. Great variation in the distribution of perspiration is commonly seen. The urinary output during treatment is always low; 300 c.c. is an average amount. It is of high specific gravity. A decrease of urinary nitrogen output is constantly found and the urinary phosphorus output is also usually lessened.

The respiratory metabolism is always greatly increased, varying from an increase of 25 to 175 per cent of the normal rate. The basal metabolic rate increases practically 7 per cent for each degree of rise in temperature. Of practical interest, the French school has utilized the profound stimulation of metabolic processes in association with dietetic safeguards as a ready means whereby to control the problem of obesity. Similarly, the sluggish metabolism of the inactive may readily be brought

under effective control. The effect of an elevated temperature in stimulating metabolism to the point where waste and toxic products are so completely metabolized as to be rendered entirely innocuous may explain, in part, the beneficial effect of fever therapy in certain allergic states. As treatments are administered regularly, the body appears to maintain adequate compensation, and the reactions excited are well within normal physiological limits.

THE INHERENT ADVANTAGES IN HYPERPYREXIAL THERAPY

The advantages are many. With careful selection of cases and proper administration there is no accompanying mortality. This sharply contrasts with the 5 to 10 per cent mortality which is found in malarial therapy.⁷ A great advantage in electropyrexia is that it is available whenever desired and that the frequency of application as well as the length and intensity of treatment are under complete control. We can thus modify the treatment as required for each individual case and completely control it. In this method, in contrast to malarial and foreign protein therapy, not only are normal processes stimulated, but, further, the blood complement is not depleted nor are the immune reactions disturbed.⁸ In many diseases electropyrexia provides a formidable weapon where heretofore we have had practically nothing to offer. In addition, there are many distressing diseases such as cancer, neuritis and arthritis, in which by the use of fever therapy we are able to modify and frequently to provide quick relief of pain. Drugs can be used in conjunction with fever therapy and thus improved results may be obtained.

THE CONTRAINDICATIONS TO TREATMENT

Electropyrexia is not entirely devoid of danger, and certain well-recognized indications must be scrupulously observed if disaster is to be avoided. Properly carried out, it becomes free of all danger. Where physical resistance has been greatly depleted by chronic disease, care is necessary, for example, in the presence of active pulmonary, cardiovascular and renal disease. Thyrotoxicosis, advanced arteriosclerosis, chronic hypertension, pulmonary œdema, weak or irregular heart action, cyanosis, pallor and

an unbalanced thermo-regulative centre suggest hazards which must be accorded greatest respect. A pulse rate over 150, respirations of 40 or over, a systolic pressure of 95 or less, and a blood urea of 70 or over, similarly demand caution. On hot, humid days, the danger from heat exhaustion must not be disregarded, although this danger is not so great as where external heat is used as a means of inducing fever. Areas of skin anæsthesia must ever be protected against excess heating.

DISEASE PROCESSES WHICH HAVE RECEIVED MAJOR STUDY

Those diseases in which the use of electropyrexia has been most carefully studied are cerebrospinal syphilis, disseminated sclerosis, infective arthritis, acute and chronic gonorrhœa, and certain allergic states, such as asthma, urticaria, hay fever and hyperæsthetic rhinitis. More recently the use of electropyrexia in chorea, septic endocarditis, myocarditis, acute poliomyelitis, the pneumonias, *Br. abortus* infections, acute and subacute rheumatic fever, acute influenza and the nephritides has received intensive study and has shown considerable promise. These conditions are varied and at first sight seem to be totally unrelated. In the main, however, they have this in common that they are not self-limiting and they are not associated with a marked sustained increase in temperature. Since the value of fever as part of the defensive mechanism is now well-recognized it may be that electropyrexia provides a type of defence which is otherwise lacking.

Dementia paralytica.—Reports on the results of treatment of hundreds of paretics by electropyrexia are now available, and it appears highly probable that malarial treatment will shortly be superseded.^{9, 10, 11} In both the end-results and in its susceptibility to control and standardization electrotherapy has distinct advantages. Reports from different clinics, however, are conflicting and indicate the necessity of exact technical procedures and the proper selection of cases. Late cases with marked deterioration cannot be expected to give as good results as early cases. This is well seen in a recent study by Neymann, who found that 64 per cent of his cases made entirely satisfactory social adjustments, and a further 8

per cent were so greatly improved as to require but the slightest supervision in their homes. Twenty-eight per cent showed no improvement, but in this group all the cases were advanced and many showed complete deterioration. In all treated cases, prior to treatment, the spinal fluid showed an increased cell count, a positive Pandy reaction, a four-plus Wassermann and a typical colloidal gold curve. The average period of hospitalization was three months. Of practical interest is the fact that the final serological findings do not necessarily coincide with the clinical improvement. In Neymann's experience the remission periods and the rates of improvement in cases treated by inductothermy definitely exceeded the results obtained in cases treated solely by malarial inoculation. As originally used, the treatment consisted in the maintenance of a temperature of 103.5° for six hours, and, where possible, 105.8° for an extra two hours. Many cases will be found in which much more vigorous treatment can readily be given. With many the treatment can readily be given as an ambulant procedure.

Wassermann-fast subjects.—In this condition the association of fever therapy, iodine and bismuth has proved of great value. Potter, of San Francisco¹² thus describes his procedure. "In this, 5 c.c. of Loesser's intravenous bismuth are followed by electropyrexia and the production of a temperature of 103° for two hours. Forty-eight hours later 2 c.c. of Burnham's intravenous iodine are given and again a temperature reaction is excited. According to the patient's reaction, 10 to 12 such series of treatments are given. Tryparsamide may be given in association, but the eye grounds must constantly be kept under close observation."

Multiple sclerosis.—Multiple sclerosis has similarly been extensively studied by Neymann and Osborne, and recently they have reported upon 25 cases.¹³ In their report they cite the incidence of this condition as representing from 7.5 to 10 per cent of all cerebrospinal organic lesions. Certainly, any form of therapy which tends to arrest the progress of this most insidious and intractable malady becomes worthy of our most serious consideration. Forty per cent of the treated cases showed marked improvement under electrothermia and another 40 per cent showed improvement in

lesser degree. Many of the cases were of very long standing, but even in this group remarkable remissions were secured. The results obtained may be due to the effect upon metabolism, and upon the intensely activated capillary circulation, or they may follow a direct action on the hypothetical causal organism. While the mechanism is open to question, the results are definite. Treatments are given bi-weekly to weekly; they are of eight hours' duration and the temperature is maintained between 103.5 and 105°. In no case should the latter figure be exceeded because of the very definite danger of upsetting the heat-regulating mechanism, which is often very unstable. A rapid pulse (over 160), and rapid shallow respirations or cyanosis are indications for the immediate interruption of treatment.

Other organic nervous conditions which have been treated to advantage, are Parkinson's syndrome, subacute combined degeneration, and encephalitis lethargica.

Arthritis.—In chronic non-specific arthritis electropyrexia is not offered as a cure-all nor as a method which should supplant already recognized procedures.^{10 to 13} It is advanced as a method of treating selected types of intractable cases, and experience has shown that a large percentage show very definite improvement. The infective group show the most favourable response. With proper selection, 70 to 80 per cent of treated cases will show a marked remission of symptoms. The treatment prescribed is that of 104° degrees for eight hours. Treatments are given bi-weekly to weekly, according to the indications present. Except for the day of treatment many of these patients are entirely ambulatory. Eight to twelve treatments constitute an average series. In the degenerative group of arthritis cases the treatment must be administered with the greatest caution. This obtains because of the high incidence of cardio-renal disturbances which is encountered. In acute gonorrhœal arthritis the Mayo Clinic has shown 90 per cent of cures. Of the chronic cases 40 per cent were cured and 30 per cent very markedly improved.

Asthma and allergic states.—In intractable asthma and in certain other allergic conditions, such as urticaria, hay fever and hyperesthetic rhinitis, electropyrexia has been used to de-

cided advantage.¹⁰ Forty-two cases of chronic asthma have been summarized by Feinberg, Osborne, and Steinberg. These cases had all been exhaustively studied and every known form of treatment had been employed without apparent results before fever therapy was tried. In 51 per cent of the cases treated by this means complete remissions were obtained and in another 29 per cent, marked improvement. A temperature of 104° at four-day intervals for two treatments constitutes a series.

Gonorrhœal vaginitis, urethritis and cervicitis have been cured by but a single treatment. Where indicated further treatments are given at four- to eight-day intervals. In cases failing to respond to all other measures, Warren and Wilson have successfully used temperatures of 106.5° for a five hour period. In all refractory cases of gonorrhœa which do not respond to accepted therapeutic measures there is definite indication for hyperpyrexia. The Mayo Clinic has reported 85 per cent cures in gonorrhœal infections involving the urethra, vagina, cervix and Fallopian tubes.^{14, 15, 16}

Other states benefited by electropyrexia.—Selected cases of both acute and chronic bronchitis rather consistently show a favourable response to pyrexial treatment. The pain and distress associated with acute pleurisy are usually relieved in but one or two treatments. The influenzal state almost invariably shows rapid responses to single moderate dosage. Intractable neuritis of unknown origin not infrequently responds to repeated moderate dosage. Marked analgesic effects often follow the first treatment. Chronic pneumonias, other than tuberculous, have very frequently shown immediate benefit and not uncommonly prompt resolution ensues.

The treatment of both lobar and bronchopneumonia by means of inductothermy frequently yields spectacular results. Such a result is seen in the accompanying chart (Fig. 3). The first treatment was given at 2 p.m. on the second day; a second treatment was given at 8 p.m.; the third treatment was given at 8 a.m. on the third day. At this time a typical type of response is in evidence. Subsequent treatments in the case are seen in the heavy vertical lines at the top of the chart. With proper selection, it is our experience and the testimony

of older and much more experienced workers that such results should routinely obtain. That they are not a matter of spectacular coincidence is well established. The type of infecting organism present does not appear to materially influence the end-results of treatment. Dr. Milton Schmitt, of Chicago, has been largely responsible for the pioneer research work in this field and has made a most meritorious contribu-

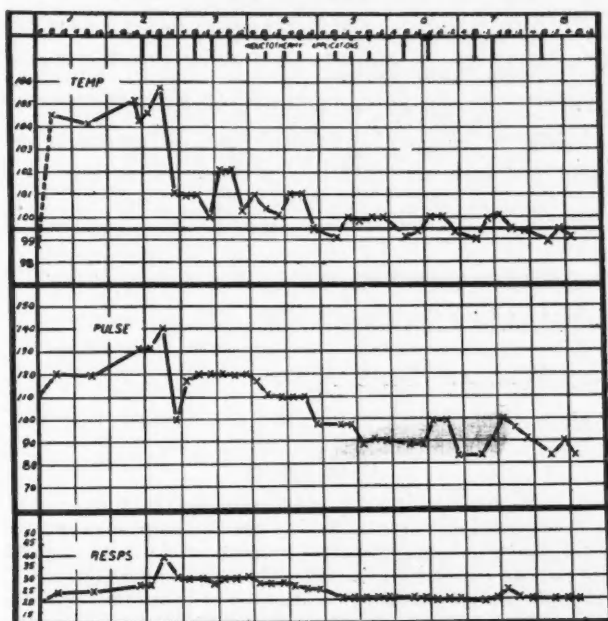


Fig. 3.—Lobar pneumonia chart.

tion. In our own department some 379 treatments have been given in 53 cases of pneumonia.

In the measure that treatment is instituted at the earliest possible stage in the disease success will be registered. Failure in securing prompt and favourable response largely appears to depend upon complications which have not been recognized. In the total group of cases it becomes all important to exclude from active treatment those which show undrained empyemas and abscesses. Myocardial integrity is a primary necessity. Patients who show marked prostration are poor subjects. In the case of pulmonary oedemas special precaution must be taken. Literally, drowning may readily be precipitated. In all cases repeated x-ray examinations are invaluable in assisting to chart the therapeutic course which is to be followed. In pneumonia and the associated complications inductothermy is locally applied and without cabinet insulation.

In selected cases of peripheral ischaemia, such as is found in Raynaud's disease and in arteriosclerosis, hyperpyrexia treatment appears of definite benefit. Functional conditions which are associated with unbalance in the autonomic nervous system are usually benefited by carefully administered hyperpyrexia. Such treatment appears to assist in restoring normal balance. The tremendous stimulus to autonomic nervous system function which the hyperpyrexial state invariably excites appears to make provision for this accomplishment. In association with minimal doses of x-ray therapy, it has been our experience that electropyrrexia produces most satisfactory results in acute otitis media and in early cases of acute mastoiditis. It is our present belief that such treatment becomes the treatment of election in early cases and that the appearance of complications can in no small measure be definitely prohibited. Seven consecutive cases so treated in the present month have evidenced quick relief from all distressing symptoms, and satisfactory resolution has followed.

While modern irradiation methods are increasingly bringing the so-called radio-resistant malignant tumours under more effective control testimony is accumulating that fever therapy may shortly prove of service in increasing the radio-sensitivity of the more resistant types of tumours.

CONCLUSIONS

1. That hyperpyrexia definitely stimulates certain fundamental physiological processes which appear to be essential to the resolution of many pathological states cannot be questioned.
2. At least in part, the bactericidal effect of the fever which is excited, the elaboration of immune bodies which is facilitated, the marked metabolic stimulation which constantly obtains, and the very marked vascular reactions which are constantly in evidence are very tangible factors which assist us to appreciate the mechanisms of electropyrrexia.
3. That inductothermy constitutes a very marked advance over many of those time-honoured procedures which have heretofore been used to produce artificial fever appears obvious.
4. It is not suggested that this type of treatment is specific, but it is definitely stated that

electropyrexia provides a most effective therapeutic agency which is competent to produce beneficial effects in many instances in which heretofore our efforts have been of little value. By no means should older accepted measures of treatment be abandoned; quite frequently their association is vital. The harmonious coordination of all helpful therapeutic measures should characterize this undertaking as in all other rational therapeutic procedures.

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THE PREVENTION AND TREATMENT OF KERATITIS NEUROPARALYTICA BY CLOSURE OF THE LACHRYMAL CANALICULI*

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THE present methods of treatment of neuro-paralytic keratitis, though effective, are cumbersome. They interfere with vision and are a nuisance to the patient. Reduction in tear secretion is a recognized feature in these cases. Because of the inadequate supply of tears evaporation leads to dryness and corneal damage. Any measure preventing drying leads to healing. Verhoeff¹ kept the affected eye moist with Ringer's solution and the corneal epithelium was rapidly restored. Suturing the lids reduces evaporation of tears and clears up corneal lesions. Castor oil, liquid paraffin and vaseline serve the same purpose, as does also the Buller's² shield or special protective goggles.

Our studies have convinced us that although the cornea is anæsthetic it is the diminished tear secretion which is the primary factor in the evolution of these corneal lesions. Blocking the canaliculi prevents the escape of tears into the lachrymal sac and should help to prevent drying. In one case with neuroparalytic keratitis this was done, and the corneal lesion healed promptly.

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CASE REPORT

H.M., an intelligent woman, aged 35 years, developed a neuroparalytic keratitis in the anæsthetic eye six months after the right posterior root of the fifth cranial nerve was cut for an intractable trigeminal neuralgia, through a sub-occipital craniotomy approach. When she noticed that emotional tearing was greatly diminished in this eye, she observed the eye more closely from day to day and became convinced that it was constantly less moist than the left eye. Once after the use of a warm blower to dry the hair the conjunctiva became injected. The corneal lesion developed following exposure to extreme cold. As it failed to heal promptly the lids were sutured together and the keratitis subsided, leaving extensive corneal scarring. When she returned to our care the lids had been closed for seven months.

Direct observation verified her impression that the eye was dry, but it was obvious that some tear secretion was present. The adhesion of the lids was divided so that more complete examination could be carried out. There was extensive central scarring of the cornea in the anterior layers; the conjunctival vessels were injected, especially on the nasal side; and vision was 6/30 with correction. Measurements proved that tear secretion was present on the involved side but it was only one-sixth of the amount in the left eye.

Both canaliculi of the right eye were closed by electrocoagulation. They remained blocked for two days, during which time the eye was wet. On the third day the eye appeared dry again and the canaliculi were proved to be open by syringing. With the drying that followed, pitting of the epithelium was first noticed. The lower canaliculus was then slit by the actual cautery and it became permanently closed. The eye was more moist but not so much so as it had been immediately following electrocoagulation of both canaliculi. Therefore, the upper canaliculus was subsequently treated with the actual cautery. Though this did not close the canaliculus permanently it produced an ectropion of the punctum which effectively blocked drainage. Since then the eye has been wet but not too troublesome; the pitting of the epithelium has disappeared, as has also

the congestion of the conjunctival vessels. The subjective sensation of discomfort, present even when the lids were sutured and during the time when the eye was dry, is no longer noticed. She was aware of an improvement in vision which is now equal to 6/15 with correction.

The satisfactory result following closure of the canaliculi has been maintained over a period of five months. It is comparable to the results described by Beetham,³ after he had closed the ducts in patients with filamentary keratitis. Although closing the canaliculi would seem to be a simple procedure, owing to the fact that sensation is lost and no anæsthetic is required, the canals tend to become patent again. When the canaliculus was slit with the actual cautery it closed permanently, and therefore such a procedure would seem to be the one of choice.

The incidence of neuroparalytic keratitis after complete section of the posterior root or destruction of the ganglion by alcohol is very difficult to determine, as it may occur many years after the therapeutic intervention. Wilfred Harris⁴ thinks it probably occurs in about 20 per cent of the cases. Other authors think that 10 per cent is a fair estimate, but both these percentages seem high to us. If the important factor in the development of the corneal lesions is diminished secretion it should be possible by detailed physiological tests to select the cases in which this complication is apt to develop and to prevent it.

We have studied the lachrymal and parotid secretion in every patient who has been operated on for trigeminal neuralgia in the past year. Tear secretion has been measured by placing twisted absorbent cotton pledgets in the internal canthus of each eye so that they cover both puncta. They are allowed to remain *in situ* for five minutes. The difference in weight in milligrams before and after insertion is taken as an index of the amount of secretion. To simplify the procedure and make it as accurate as possible the dry cotton pledgets are placed in glass weighing jars with ground glass stoppers and weighed. The pledgets are then removed with forceps from the jars and placed in the eyes then returned to their respective jars and covered with the ground glass stoppers to prevent evaporation, and weighed immediately. We have used the Sartorius analysis suppression scales which weigh to one-tenth of one milligram, and they are always operated by the same technician. For the measurement of parotid

secretion exactly the same technique has been used, except that nasal tampons are placed over Stenson's ducts, as suggested by Poth.⁵

When repeated tests are carried out on the same patient the results, as might be expected, have varied. We have obtained, however, definite information as to the presence of secretion and a fairly accurate impression of its amount. We have felt that the weighing method, done properly, is more valuable than Schirmer's⁶ test with filter paper. It has been surprising to find that the secretion from the parotid gland was usually reduced on the affected side when the lachrymal secretion showed reduction. Since this measurement is a coarser procedure causing less discomfort to the patient it may eventually prove to be the more valuable test, but more data are required before this conclusion can be drawn.

The problem of the secretory nerve supply to the lachrymal gland need not be considered here. It is as complex as that of the parotid gland, and our studies on patients have not served to clarify it. For example, Verhoeff's hypothesis that diminished tear secretion is due to injury of the greater superficial petrosal nerve is contradicted by the case we have reported. In this case neither the greater superficial petrosal nerve nor the facial nerve was injured yet there was diminished lachrymation and keratitis developed. If the sensory loss were the all-important cause the lesions should appear as a complication much more frequently than they do. We can see no reason for accepting a so-called trophic influence as first suggested by Magendie⁷ and more recently advanced by Tagawa.⁸ This complex theory has no adequate proof in our opinion.

Another example of keratitis due to drying is keratitis e lagophthalmo. It is seen very commonly in the comatose patient who lies with the eyes open or only partially closed, with no blinking and no conscious discomfort. Corneal lesions seldom develop after 7th nerve paralysis. Although the patient does not wink, the discomfort which drying causes stimulates him to roll the eye up under the lid and thus moisten the cornea. The drying of the cornea occurs chiefly during sleep, but even then the eye tends to roll up so that the cornea is partially covered. The lack of winking and ectropion of the lower punctum present after seventh nerve palsies,

with the consequent damming back of tears, must also be a beneficial factor.

Years ago Magendie observed in animals that the eye in which keratitis developed following section of the fifth nerve was dry. He dismissed drying as the cause of the lesions, because when he took out the lachrymal gland in other animals corneal lesions did not develop. It is now recognized that corneal lesions do not develop after excision of the lachrymal gland, because the secretion of the accessory lachrymals, such as Krause's glands, is usually adequate. In keratomalacia though the eye appears to be dry this is not really the case.

The occurrence of keratitis after total rhizotomy for the relief of trigeminal neuralgia is such a serious complication that the following routine is suggested. Oil should be dropped in the eye immediately after operation and a Buller's shield applied. The shield should remain in place until it can be determined that the eye is not dry. If tear secretion is adequate to prevent injection of the conjunctival vessels when the eye is left uncovered and every precaution is taken to avoid trauma no complications are to be anticipated. These

patients are discharged from the hospital with Adson's⁹ protective shield attached to spectacles. On the other hand, if tears be greatly diminished and the conjunctiva becomes injected the canaliculi should be closed. This procedure causes no deformity and no special inconvenience. The conjunctival injection should be considered as an elective indication. Corneal pitting or loss of epithelium makes closure of the canaliculi an operation of necessity. Our experience with one case would suggest this to be adequate. Should it fail, tarsorrhaphy is imperative.

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NOTES ON THE MENOPAUSE*

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"I can very confidently announce one or another law, which throws itself into relief and form, but I am too young yet by some ages to compile a code. I gossip for my hour concerning the eternal politics". (Emerson—*Experience*).

THE climacteric is a critical stage in the life of woman, if one heeds the original derivation of the word. Not only is it critical for our female patients but it is almost as much so for their physicians. For centuries this epoch has presented the doctor with some of his thorniest problems, and even today, when the endocrine hieroglyphs of our lives are being rapidly deciphered by new Champollions, it is still the critical test of his skill and his up-to-the-minute knowledge. The term menopause refers to the cessation of the menses, and is perhaps a better

term, although the symptoms so characteristic of this period often begin before and continue for years after all gross evidences of menstruation have disappeared. If "change of life" were not so roundabout a phrase it might be the most suitable term of all those mentioned to date.

SYMPTOMS

At some time between forty and fifty years of age, rarely before, occasionally later, the menses cease. They may cease suddenly or gradually, may stop for a month or for several months, only to recommence. The periods may suddenly become much more profuse than before, presumably due to the development of follicular cysts, or there may be spotting of blood between the menses. In general, it seems that women who demonstrate active ovarian function by the early onset of puberty or fre-

* Read at the Academy of Medicine, Toronto, February 2, 1937.

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quent child-bearing manifest the same by a delayed menopause. Before the menses undergo any variations, or before their cessation at least, there may be mental or psychic symptoms such as depression, irritability, insomnia and loss of memory. More often such mental reactions succeed the loss of the menses. The symptom most frequently complained of, however, is "hot flashes". Werner¹ says that 90 per cent of his series of 197 women, of whom 53 were castrates (of an average of 27 years of age), 96 menopausal and 48 involuntarily melancholical, reported them. These flashes are "waves of heat" spreading rapidly over the body or portions of it, often accompanied by perspiration. They can be induced, very often, by immersing the hands in hot water, as when washing dishes, or under conditions of emotional stress, as when hurrying through crowds or meeting guests. The hot flashes may succeed one another very rapidly or merely occur at intervals of days. Some women complain of headaches, tinnitus, dizzy spells, faintness, palpitation, cold limbs. True psychoses may develop. In Werner's series 21 per cent of the castrates and 35 per cent of the natural menopausal displayed psychoses. Arthritis is a not uncommon occurrence. There is no consistent variation in libido. A tendency to increased weight and the deposition of fat at the waist, pelvic girdle and thighs, may show itself. This may be associated with evidence of hypothyroidism, hypopituitarism, or merely be due to more sedentary life.

Kelly states that the impression is general that the severity of menopausal complaints is most marked in cases of surgical castration in younger women. Peterson, basing his remarks on a questionnaire sent to 173 women of all ages who had been castrated, said that only 10 per cent of them escaped these symptoms, and found no consistent variation between various age groups. However, Culbertson,² in a good review of the relevant literature on this subject, found many conflicting opinions. He remarked that he had castrated 24 young women between 15 and 25 years of age approximately, was able to follow up 9 of these, or 40 per cent, and found that none had severe castration symptoms and few had any at all. Maranon³ found that the secondary disturbances of the menopause were more turbulent, but briefer, the closer it came to the critical age of 40 years. Novak⁴ supported

Culbertson's opinion. This question is of great practical importance and one should point out that it is still open to controversy. At one time I worked under a gynecologist, trained under Culbertson, who felt so strongly that the symptoms in young castrates were rarely very troublesome that he seldom operated upon one inflamed ovary in a young woman, but he removed both completely. We had little subsequent difficulty with complaints from these patients. This is not to say that one can recommend radical ovarian surgery in young women. I am well aware of the emotional problems involved and the importance of preserving the function of child-bearing. I merely raise the point for discussion— Do young surgical or x-ray castrates have as severe menopausal symptoms as do older castrates? What cases of x-ray castration I have seen have given me the impression that their symptoms are more severe than those of surgical castrates. If I have stated the facts correctly, this consideration must be borne in mind when suggesting x-ray therapy for fibroids at the menopause, and, together with other considerations, has caused gynecologists of late years to treat them surgically as a general rule. Presumably the x-ray acts principally upon the ovaries. In surgical castrates, be it noted, there is usually a latent time before hot flashes and sister symptoms appear.

PHYSIOLOGY

At the menopause the breasts display an atrophy of glandular tissue with replacement by fat and fibrous tissue. The acini vanish and only the main ducts persist or become cystic. The vulva becomes thin and atrophic, with sparse hair. The vaginal epithelium becomes thin, shiny and atrophic. It may secrete a thin, serous, irritating discharge. The vaginal fornices become obliterated or synechial bands spread across them to obliterate a part or all of the vagina. An intensely acute vaginitis may develop, which keeps the patient's mind from all else — and this seems especially frequent among x-ray castrates. The uterus undergoes a symmetrical atrophy, or the cervix undergoes an atrophy more marked than that of the corpus. The vessels show marked arteriosclerosis. The endometrium becomes thinned and consists largely of stroma and small, shallow glands. Where fibroids are present they may degenerate at this epoch or may actually increase in size.

In most instances they remain of the same size or become smaller through the ensuing years. The tubes become smaller, as do the ovaries, which may shrink to the size of a bean. Corpora lutea are no longer found and the corpora albicantia disappear in time. The ovarian cortex becomes dense and sharply demarcated. This may be a factor in hindering follicular rupture and so eliminating the luteal phase of the menstrual cycle.

That there are exceptions to the rule is apparent in any group of cases studied. Just as pregnancy can occur in amenorrhœic young women, so it may occur after the cessation of menses at the climacteric. It would seem that true ovarian and uterine function continues longer than the menstrual cycle in such women. Kelly cites the patients of Batley and Pitou. The former was a woman menstruating regularly at 93 years of age. Pitou's patient was a woman who had regular menses for six months at 72 years of age, became pregnant, and aborted at the second month (with recovery of the fetus, all ye who doubt!). Maranon³ cites Donizetti's case of the climacteric at 79 years of age, and Raciborski's finding of a case in the Memoirs of the Academy of Sciences in 1778 of a woman aged 106 who still menstruated. He also mentions Depasse's case of a menopause at 59 years, followed by a delivery at the age of 68 years. Of course, menstruation unduly prolonged or recurring after the menopause would make one suspect granulosa cell ovarian tumours nowadays. That it may be due to cervical polypi, for example, is illustrated by a case of Scanzoni's quoted by Maranon. Frank, in his Text-book of Pathology, figures a Graafian follicle from the ovary of a woman aged 62 years whose menopause had occurred twelve years earlier. The ovum and granulosa layers appear perfectly normal. There are a few theca interna cells and the stroma is very fibrous. Everyone is aware of, if not familiar with, the story of Sarah. We are informed that "it ceased to be with Sarah after the manner of women", for she was 90 years old. Yet she bore a son at that ripe age. I well remember seeing in the laboratory of Professor G. W. Bartelmez, of Chicago, a microscopic preparation of an ovary. When I first saw it and knew nothing of its history I thought it was the ovary of an adult macacus monkey. Judge my surprise on learning that it came from a woman aged 103 years.

This specimen he has never reported, but I can say briefly that it was very small and contained in a very dense stroma peripheral follicle-like structures, probably proliferations from the germinal epithelium. There were no primordial follicles in any section, but there was a typical corpus albicans, which in the sections available measured about 2 mm. in diameter. This must imply, surely, that the ovary had functioned not very many years previously.

THE PSYCHE

Before a discussion of the endocrinological problems involved is begun, a few words on the psychic colour of the menopause will be in order. The term "involutional melancholia" has been coined to describe a group of women who become more or less psychotic at this critical period. No doubt these women are victims of an unfortunate heredity and have been exposed to some basic and well-marked secondary strain. Life-long habits of pessimism or self-pity in egocentric personalities predispose to these breakdowns. These women look back, often enough, to disappointed hopes and ideals, find the lot of their fellows to be envied, feel lonely as husbands die or children leave home to form other households, feel left behind in the economic struggle. Tradition has focussed these women's attention on the menopause—a certain loosening of personal controls seems justifiable then, and, once let slip, these are hard to regain. More of this later!

THE ENDOCRINE BACKGROUND

We have come very recently to appreciate that the moving finger which writes these minutiae on the page of life is endocrine, and subtle in its manifestations. In the effort to clarify these let us discuss three glands, omitting the adrenal (which seems to have a definite rôle, however), and two fluids, the blood and urine.

The thyroid may become more active or less active after the menopause, and which of these alternatives actually develops seems to be determined largely by the previous trend of the individual. Several authors have found that castrated animals show an increase of colloid and a flattening of the acinar epithelium. Geist and his associates, however, found no permanent change in the basal metabolic rate following bilateral oöphorectomy in 48 women—although

16 showed a weight gain of 4 to 26 pounds. Werner confirmed this general observation. At the menopause the so-called "castration cells", which are modified basophils, appear in the anterior hypophysis, accompanied by an increase of ordinary basophils. Normally in the fifth decade the hypophysis decreases in size, but in castrates on the contrary, as observed by Fichera in 1905 and confirmed by Tandler and Grosz, it enlarges. Normally, there is no eosinophilic infiltration of the pituitary, but after x-ray castration this occurs.

The pituitary changes are reflected in the urine, and after an interval of approximately six months no more prolactin B or luteinizing factor is found there, but only prolactin A or maturation factor. This latter may be found for many years. There is this peculiarity of x-ray castration, that it is not accompanied by an excretion of prolactin A for as long as one to one and a half years after castration—then this continues for about eighteen months. The reason for this is not known.

The ovary undergoes definite functional changes, but these are probably much less marked than was formerly thought. It was in 1870 that Waldeyer stated that within a few years after the menopause the follicular structures atrophy completely. Since that time this has been taken for a truism. But just as before puberty there is follicle development and oestrogen production, so ovarian function often continues after the cessation of menstruation, whether in periods of amenorrhoea in full sexual life or after the climacteric. However, the ovaries probably become less responsive to the pituitary, just as the ovaries of rats less than eighteen days old cannot be stimulated by any amount of anterior pituitary hormone,⁵ and such defect seems to be inherent in the ovary itself.

The blood and urine continue to display a definite content of oestrogen for the first three years of the post-menopausal period, and occasionally much longer. Frank⁶ cites an instance of a normal blood oestrogen cycle occurring fully 17 years after hysterectomy. Robson⁷ and others found that substantial amounts of oestrogen were excreted in the urine even 18 years after the menopause. Papanicolaou and Shorr cite cases of regular oestrous cycles in human vaginal epithelium after the menopause, and

note that the smear does not seem to be well correlated with the symptoms. Schlossberg and Durruty⁸ state that in 21 tests made on the sera of three castrates and three cases of natural menopause oestrogen was found 15 times, and in quite high concentrations 8 times. Fluhmann⁹ reported that of 8 surgical castrates (five weeks to ten years after castration) 4 displayed normal blood oestrogen curves and 4 had a constant but low oestrogen content. Of 7 menopausal women 5 had normal blood oestrogen curves and 2 of these were one to three years past the menopause. The other two showed a constant low content of oestrogen. In a series of 24 surgical castrates, 11 roentgenological castrates, and 10 natural post-menopause cases, Salmon and Frank¹⁰ found that in only 40 per cent of the 45 women were the vaginal smears uniformly negative for signs of oestrogen. In 30 per cent of the cases there were variations, sometimes oestrogen and sometimes not. In the remaining 30 per cent there were always oestrogen smears. Tate observed that women at the menopause whose periods had been absent as long as five months might pass urine which when injected into mice produced oestrous uteri. Novak and Yui¹¹ have recently published interesting studies of the same general tenor. Of 804 women curetted one to twenty-four years after their last menstruation 40 showed typical endometrial hyperplasia. But in the 19 instances in which they were able to study the ovaries of these 40 women the structures were typically senile. These authors observe that Breipohl, in 130 cases curetted one to twenty-five years after the climacteric, found endometrial activity in 31 and hyperplasia in fully 15 of that 31. Frank *et al.*¹² have shown that of 12 surgical castrates all excreted appreciable amounts of oestrogen in the urine. There was no correlation between the amount of oestrogenic substance excreted in the urine and the blood oestrogenic content in the only two cases studied by them, nor between the urinary oestrogen and the hot flushes, arthritis and similar menopausal symptoms, nor between the urine oestrogen and vaginal spreads. In only 2 of the 5 cases of physiological menopause studied was the excretion of oestrogenic substance nil, and yet one of these showed oestrogen in the blood. All had marked menopausal symptoms.

That menopausal amenorrhœa is not unlike the secondary amenorrhœas of active sexual life is illustrated by Fluhmann's published analysis of his seven cases cited above. The same point is accentuated dramatically by such reports as that of Huebscher's case, a woman 80 years old whose uterus was made to grow, display a secretory endometrium, and menstruate, by the use of large doses of oestrin. Similarly, Zondek implanted bovine anterior lobe tissue into senile mice which had not been in œstrus for several months, and found œstrus, enlarged ovaries, large follicles and numerous corpora lutea resulting.

Albright has pointed out that hot flashes are not correlated with the urine content of œstrogenic substance nor yet accurately with the prolactin A content. He suggests that the prolactin A is the more likely cause of these particular symptoms, however, although his data as presented scarcely support this conclusion. Indeed, there seems to be nothing in the literature to suggest any unvarying relation of the various complaints of the menopausal period to individual endocrine factors. For example, the same menopausal symptoms may be found when the œstrin is low as high, and may be successfully treated respectively by œstrin or its withdrawal. Hot flashes may subside upon the administration of œstrin or its antagonist, wheat germ oil. Therefore, clinical considerations by themselves will scarcely determine what the proper therapy for any given case should be. The impression one receives is that each woman reacts to the crisis of this time in an individual way, which is partially determined by the many incidents and factors that have moulded her personality and now compose it in aggregate, and partially as well by the fluctuating endocrine background.

THERAPY

Let it be made clear that perhaps two of every three women who pass through this epoch have either no complaints or such trivial difficulties that no treatment is indicated. Women should be taught to expect no upset at the menopause by those best qualified to impress this fact upon them with authority, viz., their medical consultants. Not every one who falls on the ice breaks his hip, and because the occasional person does so let us not overstress the dangers of

walking abroad. When, however, a woman comes to this period of life, and feels that, in the words of a favourite Canadian poet:

"Relentless as the malison of Zeus
Is Time's dark judgment on our fleeting days;
All scrutinies of fortune but deduce
Poignant impermanence of works and ways,
Like arrows shot by twilight or like haze
Across the deep."

Feels that she requires

"A writ to turn back Time's un pitying officers."

Then must this experienced and sympathetic advisor rally his powers to direct his patient in her stormy passage. He must minimize past failures and discouragements and set before her new goals and aspects of the ripe years. Point out, with Emerson:

"Every man's task is his life-preserver. The conviction that his work is dear to God and cannot be spared, defends him."—(*Worship*).

Browning has a hint for us in Rabbi Ben Ezra:

"The best is yet to be,
The last of life, for which the first was made

Young, all lay in dispute; I shall know being old."

Kelly wisely says:

"It is the encouragement to remain in the traffic stream of life that holds for them the best chance of continuous nervous stability."

Sedatives reinforce these efforts, but have dangers of their own, like other crutches. Recently Cross in Canada, as well as Barbour, Pilkington and Sargant¹³ in England, have pointed out that therapeutic doses of bromides may be cumulative and toxic in just such cases as this age group often presents, e.g., arteriosclerosis, anæmia, renal or cardiac disease. Hannan has stressed that the "depression" of menopausal patients is often ascribable to just this sort of bromide intoxication. It would seem, therefore, that the barbiturates offer more in these cases than do bromides. Beckwith Whitehouse¹⁴ and Esch have suggested blood letting at intervals, apparently on the assumption that since menstrual hæmorrhage has ceased, a substitute for it should be found. No experimental work has been done to support this viewpoint, and perhaps it will prove to be as fallacious as letting blood in eclampsia.

The evidence appearing earlier in this paper indicates that there is a very doubtful and variable correlation between the amount of œstrin in the blood and in the urine. Probably

this is as true at the menopause as during active sexual life.^{9, 15, 16, 17} There is little to be gained, therefore, by studies of the urinary œstrin in these cases. For a similar reason there seems to be little value in Papanicolaou's method recently proposed for following their changes in the vaginal epithelium. The studies of prolan excretion seems to have led nowhere. The only thing that remains, indeed, is therapy based upon repeated estimations of blood œstrin.^{18, 19}

Periods of amenorrhœa during active sexual life may be characterized by either an œstrin cycle in the blood, a continuous low concentration of œstrin, or a persistent absence of an appreciable œstrin content.⁹ In the same way post-menopausal amenorrhœa, natural or induced, apparently may show the same characteristics. As the first two types appear to be amenable to attempts at œstrin withdrawal, and the last type demands œstrin therapy, it is important to analyze the patient's blood periodically in order to determine in which of these three groups she should be located. Analyses made every five to ten days should determine if a cycle is present. If present, the mistaken administration of œstrin preparations will probably aggravate her complaints very grievously for four or five days. If absent, however, œstrin may be given, and the size of the dose, frequency of administration, and duration of treatment will be found to vary with each case. Therapy in any menopausal case should be kept up, if possible, until it is no longer needed. A suggested dose that helps many of these patients is 2,000 rat units every three to five days.

Patients who already possess an œstrin excess, and these are numerous, be it remembered, often exhibit a hypothyroid syndrome, and respond favourably to doses of thyroid extract or thyroxin. Wheat germ oil is a valuable auxiliary in selected cases, especially when there is a high œstrin vaginitis.

From a small group of 77 menopausal cases with which I have had some contact in the past three years—26 of them private cases of my own, 28 those of colleagues, and 23 clinic cases—I have culled some representative examples of various menopausal complaints, with a description of the treatment used. They will make clear many points that this paper has overlooked or stressed too little.

CASE 1*

ARTHRITIS, MYALGIA, HOT FLUSHES, EXCESSIVE NASAL DISCHARGE, HYPOTHYROIDISM

Mrs. A., a physician's wife, aged 46 years, was seen first on December 14, 1936. She had had a consistently "dripping" nose for years. Her frontal sinuses "filled up", her head ached in the region of the mastoid processes, and the pain was referred down the back of her neck. There were never any true headaches. In August, 1935, she had an acute polyarthritis, which was severest in the knees, ascended to the hips, and necessitated a period of three weeks in bed, with morphia for the worst of her pain. After that attack she experienced much pain across the lower back, and occasionally had transient pains in the hips referred down both thighs anteriorly. In the six months prior to her visit she had tired unduly, had had frequent "hot sweats" break out over her body suddenly, and had gained ten pounds weight in the last two months of that period. She always felt cold, had a very dry skin and noticed the skin driest during attacks of the lumbago. There was no constipation nor flatulence. There had been marked mental depression of late "for no reason", and hitherto she had been of a cheerful nature as a rule.

There had been several children. After the youngest child was delivered six years ago she had had a tubal ligation and uterine suspension. Before the cessation of menstruation she had had menorrhagia regularly.

On examination she showed an unusually dry and senile skin. She wore inner stockings and pads at her knees for warmth. The arteries and even the veins were very sclerosed. The vaginal mucosa was also presenile in type, thin, pale and shiny. The blood œstrin was raised above normal.^{18, 19}

She was put upon thyroid extract, one-half grain each day (P.D. & Co.). On December 23rd the skin was much improved as well as her energy and temperament. The muscle pains and aches had not recurred. She was seen last on February 17th, reporting that she had had two normal menses (in December and this February). She was feeling normal in every respect but for a slight excess of nasal discharge which was not troublesome.

CASE 2

VAGINITIS AND PRURITUS

Mrs. D., aged 58 years, was first seen on May 4, 1936. For years she had been suffering from a severe Parkinsonian syndrome. For approximately twenty years this patient had had a severe vaginal irritation and occasional vulvar pruritus. When she was examined the speculum revealed some redness of the whole vaginal mucosa and marked general tenderness (so that the insertion of the speculum was very difficult) and a sessile cervical polyp, which was removed. There was no trichomonas in a hanging drop preparation. The blood test for œstrin revealed no excess, hence, either a low or normal content. As this was in May, when diets had been deficient in vitamin E for months, it was all

* I have had another such patient whose "sinusitis" and "dripping nose" was associated with a high blood œstrin and cleared up with thyroid therapy. This type of case appears to be just the reverse of the atrophic rhinitis cases which respond to œstrin therapy as recently reported in this *Journal* by Mortimer, Wright and Collip.

Somewhat analogous to their results were those I recently obtained with progynon B suppositories in the relief of a severe anal and buccal distress in the case of a woman 70 years old. This woman was unable to wear her dentures before treatment, although no abnormality of the buccal mucosa or gingivæ was discernible.

the more noteworthy that the blood content of œstrin was not increased.²⁰ We concluded that œstrin treatment should be attempted.

On May 6th she received 1,000 rat units of progynon B. There was no change. The dose was accordingly repeated on May 7th. On May 11th the speculum revealed no evidences of vaginitis, but the patient complained that the insertion of the speculum was still painful to her. The pink colour of the mucosa had changed to a definite bluish tinge which can be compared only to the most marked Chadwick's pregnancy sign one ever sees. She was put on 2,000 rat unit œstrin suppositories, in place of hypodermic treatment, and instructed to use one twice each week. On May 24th there was less blueness in the vaginal mucosa, but no recurrence of the vaginitis and no more pruritus. In fact, she felt so well that the cost of the treatment began to seem excessive and she discontinued it.

CASE 3*

VAGINITIS; WHEAT GERM OIL IDIOSYNCRASY

Mrs. E., a widow for twenty-five years, aged 60 years was first seen on March 23, 1936. This woman had felt quite well until May, 1934. Then an urethral dysuria began and continued despite bladder irrigations and medication. She had douched regularly with "blue tablets" for three months before consulting me. She had had very little leucorrhœa. Headaches and blurred eyesight were other recent developments. There had been menorrhagia, not marked, until her menopause at the age of fifty-four. The menorrhagia had been very severe during that time. She had been mentally quite depressed also.

Physical examination revealed a blood pressure of 160/80, moderate obesity, no tenderness over the bladder. There was much serous leucorrhœa, some reddening of the labia. So extreme was the vaginitis that scarcely any examination could be tolerated. The vaginal vault and portio vaginalis looked as though boiling water had scalded them. Sedative douches and general therapy proved useless. Her mental state was pitiable, as she had suffered so long and was of a querulous disposition at best.

A blood sample was taken for an œstrin test, but, expecting it to be low, 1,000 rat units of œstroform was given hypodermically before the blood was tested. The œstrin in the blood test proved to be excessive and the œstroform therapy produced so much vaginal burning that it "almost drove her mad". She had nervousness, hot flushes, felt too hot to sleep at night (April 2), and the vaginitis became much more angry. On April 6 her right inguinal glands had become painful, and she was put upon wheat germ oil to counteract the excessive blood œstrin. By the 10th she was greatly improved. By the 17th she was "better than in months". The leucorrhœa had stopped. The inguinal adenitis had almost cleared up. The vaginal epithelium was still slightly reddened but almost normal, and the vulva looked normal. By May 19th she had begun to look placid for the first time since she had been under treatment, and had no more vaginal distress nor inguinal adenitis. The speculum revealed a practically normal appearance of the vaginal mucosa, which was red no longer and not tender. Just as we thought everything was under control she developed an urticaria for the first time in her life, and all too soon it became evident that she was sensitized to wheat germ oil and could not tolerate it. I have seen four other such cases of wheat germ oil sensitivity in adults, and one in an infant whose mother was taking wheat germ oil to promote

lactation. The patient would not submit to cutaneous tests for sensitization to wheat and resorted to medical care elsewhere.

CASE 4

X-RAY MENOPAUSE, VAGINITIS, DEPRESSION

Mrs. F., aged 44 years, came to us first on June 17, 1936, at the Endocrine Clinic of the Victoria Hospital. She had had four children and four abortions. The last child was conceived after a tubal ligation done in July, 1933 (carried out for hypertension and chronic nephritis). Accordingly she received an x-ray sterilization in February, 1935. Since the x-ray menopause there had been a severe vaginitis but little leucorrhœa. Dyspareunia was marked. Hot flashes were troublesome. She had lost five pounds in weight and had become very irritable, "wanted to go away from everything". There were definite paranoid trends. There was marked failure of memory in the last two years. Almost constant headaches were noted, and these had become increasingly severe. She had "no energy" and "sore bones" in the region of the lower leg; had "cold breasts" often, she said, even in hot weather.

Examination revealed some tenderness in the lower abdomen. The corpus uteri was unusually small. The vaginal mucosa was raw, red, and acutely tender. A blood test revealed no œstrogenic excess, and as this was early in June we suspected that the œstrin was actually low. Accordingly she was given hypodermically 1,000 rat units of œstroform. There was no aggravation of symptoms the ensuing week, so she was given 10,000 rat units by injection on July 7th, and put on brewer's yeast. The hot flashes were not felt for four days after the injection, then recurred. There were very distressing dreams. The vaginitis seemed somewhat less acute. Phenobarbital was given and an injection of 1,000 rat units of œstroform. The "cold breasts" disappeared, and her mental depression began to lift, as well as the headaches. By July 28th the hot flashes were as troublesome as ever, but the headaches not very severe. She complained of sensations "as if she were swimming away from herself". The vaginitis was as severe as at first. The injection of 1,000 rat units was repeated twice in the next week, but there was no change in that week. Her basal metabolic rate on July 29th was -6 per cent. On August 4th, she was given progynon suppositories, and told to insert one into the vagina every other night. She also received another 1,000 rat units hypodermically. On August 11th the speculum revealed a complete cure of the vaginitis. The leg and ankle pains were as acute as ever, and also she complained of muscular pains in the back of the neck and left shoulder, with tenderness. Hyperparathyroidism was suspected, but x-rays of the leg bones revealed no osteoporosis. On August 11th her blood calcium was 12.5 mg. per cent, and phosphorus 3.6 mg. per cent.

She was seen next on September 21st, with the vaginitis as severe as ever. There had been no treatment since August 11th. The muscle and bone pains were as severe as ever, worse at night. She was given the progynon suppositories again, with instructions to use one twice a week. Again her vaginitis cleared up, but returned about three weeks before her next visit on November 3, 1936. Again the suppositories were used and again the vaginitis and irritation of the labia minora cleared up completely, by November 10th. We have been unable to relieve her "bone pains" by any measures we have tried.

CASE 5

ANAL PRURITUS

Miss G., aged 42 years, was first seen on November 10, 1933. Her complaints were menorrhagia and dysmenorrhœa. The cramps during menstruation were like labour pains. On examination a fibroid 2 or 3 cm. in

* I have since seen three other cases of vulvovaginitis associated with high values for blood œstrogen. All have been cured by wheat germ oil.

diameter was detected near the right cornu of the uterus. There was an apparently healed bilateral apical pulmonary tuberculosis of two years' standing. An x-ray was taken and confirmed the impression that it was healed and static. A trial of thyroid extract produced no change in the menorrhagia. A curettage was done on November 30th and revealed that the fibroid near the right cornu was submucous in location. The curettings were negative. Myomectomy was advised, as the dysmenorrhœa and menorrhagia were so severe. Operation was delayed, while osteopaths, other physicians, and an electrotherapist were consulted in turn. Finally on July 31, 1934, a tremendous hæmorrhage began at the time the period should recur. The patient was sent to hospital and there it was seen that the uterus had spontaneously inverted itself. We were unable to reduce this under ether, so a total hysterectomy was done and one ovary left *in situ*. She made a good recovery.

On November 21, 1934, there were no complaints, but a constant ringing noise in the head and hæmorrhoids had become troublesome. A chest plate revealed no change in the pulmonary status. By August, 1935, her anal pruritus was severe. As this was ascribed to the hæmorrhoids, hæmorrhoidectomy was suggested. In early August she had an emergency operation for acute suppurative appendicitis, and the hæmorrhoidectomy was accordingly delayed until late in September. She was well thereafter but for the anal pruritus which persisted with little change. Thyroid therapy and local applications were not helpful. By May of 1936 this pruritus was nearly intolerable and all local applications had failed to give relief. The skin for about one inch about the anal orifice had assumed a greyish appearance resembling parchment and very similar to that of kraurosis vulvæ. A blood test showed an excess of oestrogenic substance. Accordingly she was put upon wheat germ oil therapy on June 9th. In ten days' time there was very great improvement. She was free of pruritus for the first time in over eight months and there was a very marked reversion to normal in the appearance of the peri-anal skin. There has been no complaint since that time.

SUMMARY

1. Women should be taught to be less apprehensive of the menopause.
2. It is questionable if women who have a menopause induced early by operation or x-ray have as severe complaints as women so treated in later years.
3. The symptoms usually encountered and their physiological background are described briefly.
4. Reasons for suspecting prolonged ovarian activity in some women are given.
5. The endocrine background is discussed at length, and more evidence adduced to support the idea that ovarian activity may go on long after the cessation of the menses.

6. The paradoxical character of menopausal symptoms is stressed.

7. The psychic colour of the menopause and mental therapy are considered.

8. Sedatives, blood-letting, and endocrine therapy based upon estimations of blood œstrin are considered, and typical cases reported in detail.

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FRACTURES OF THE FOREARM*

BY GEORGE W. ARMSTRONG

Ottawa

WITH the rapidly increasing number of motor accidents, the more serious of which occur on country highways, and the greater prevalence of x-ray units in the smaller hospitals, more and more fractures are being treated by general practitioners.

I have chosen to speak on fractures of the forearm, because of the great economic importance to the patient, his family, and the community of the resulting function of the hand and forearm. This has been impressed upon me by the end-results which I have seen in my work for the Workmen's Compensation Board of Ontario. It is my aim to impress upon you that this resulting function depends largely upon the use of the correct methods at the beginning. The man who treats the patient first always has the greatest opportunity to obtain the best result; the man who treats the patient last always gets the blame for the shortcomings of the end-result.

The vast majority of fractures of the forearm can be treated by closed manipulation and plaster fixation. H. K. Sowles, in his review of the end-results of 91 fractures of the forearm at the Massachusetts General Hospital, states that during the period over which this series extended 120 patients in all were treated in the ward, but 29 could not be traced to their conclusion; during the same time 302 fractures of the forearm were successfully treated in the out-patient department. His analysis therefore embraces 422 patients rather than 91. Of this series only 41 came to open operation, and of these only 14 required internal fixation. This is an enviable record. T. A. Willis, of Cleveland, at the last meeting of the American Academy of Orthopædic Surgeons said that "Open reductions are performed in inverse ratio to the man's ability to do them". My plea today is for conservative methods, correctly carried out at the beginning, and early

recognition of the types which necessitate more radical measures.

Diagnosis can be dispensed with in one brief paragraph. Never omit examination of the peripheral nerves. Wherever a fracture is suspected, x-ray films of good quality in two directions, are absolutely essential for the patient's welfare and the surgeon's protection. Fluoroscopy is not enough. If the patient declines radiological examination his written acceptance of all responsibility should be obtained. Written records should always be kept.

For convenience of discussion we shall consider fractures of the forearm under three groups: (1) fractures of the ulna only; (2) fractures of the radius only; (3) fractures of both radius and ulna.

FRACTURES OF THE ULNA

Olecranon.—It is generally accepted that fractures of the olecranon are best treated by open reduction. The fragments are tied together with kangaroo tendon or chromic catgut and the elbow bent to 80° as rapidly as swelling and tension will permit. If absorbable sutures are used the remainder of the treatment is carried out as one would if this approximation could have been obtained by closed reduction; in other words, movement is not commenced until healing will permit.

Coronoid.—Flexion must be obtained to ensure full range of function afterward. Accurate anatomical apposition is not essential.

Shaft.—Fracture of the upper third is commonly associated with a dislocation of the head of the radius. This presents a double problem. If the elbow is flexed to the desired position the alignment of the ulna is not good. The tension of the triceps extends the proximal fragment, causing posterior convexity of the fragments. If the elbow is extended to obtain good alignment of the ulnar fragments the head of the radius is sometimes inclined to dislocate forward. Satisfactory results have been obtained by doing an open reduction of the

* A paper read at the Sixty-eighth Annual Meeting, Canadian Medical Association, Ottawa, Section of Surgery, June 23, 1937.

ulna, tying the fragments together, and then flexing the elbow to 75 or 80°. If the alignment is not all that is to be desired, the plaster may be cut throughout three-quarters of its circumference, leaving the posterior aspect intact at a point slightly proximal to the line of fracture. Then by opening the plaster pressure is brought to bear on the apex of the convexity. As the plaster is opened the deformity is corrected.

Middle and lower third.—Fractures of these areas cause little concern regarding their reduction or in maintaining the correction, but it must be remembered that non-union is fairly common in the latter. Ample time should therefore be allowed to ensure healing.

In the foregoing fractures of the shaft of the ulna no difficulty is encountered in obtaining the proper length, because this is controlled by the radius.

FRACTURES OF THE RADIUS

Head and neck.—Fractures of the head and neck of the radius according to various writers constitute 3 to 17 per cent of all fractures of the elbow joint. In children conservative treatment (i.e., closed manipulation) should be followed unless there is marked displacement of fragments. Open operation with replacement of fragments is preferable to resection. Increase in the carrying angle with relative instability follows all resections. Late synostosis occurs in 50 per cent, affecting rotation. Flexion and extension are seldom limited. In adults conservative treatment should be attempted first unless there is marked displacement and comminution.

Complete supination with the elbow flexed to 90° is the position in which reduction is accomplished and maintained. Usually three weeks is sufficient, with light active exercise during the following week or ten days. Passive movements and forceful manipulations are to be completely discouraged, firstly, because they cause pain which discourages the patient from active movement; and, secondly, they may do real damage to the healing tissue, e.g., break down the callus. If re-position of fragments cannot be satisfactorily effected by closed manipulation resection should be done early.

Shaft.—These fractures are usually designated by their relationship to the insertion of the pronator radii teres. This does not seem to

me to be of very great importance. The fact remains that, regardless of upon which side of this muscular attachment the damage occurs, one fragment is pulled ulnaward, and usually end to end apposition has been lost, which condition is difficult to correct. Proper restoration of length is the first essential. To disregard this principle is to create a radial deviation of the hand, which results in a weakened grip because of the decrease in distance between the origin and insertion of the flexor muscles, and a painful wrist, because of the alteration of the level and angle of the articular surface of the radius in its relation to the lower end of the ulna. Proper length of the radius must be re-established, even if this requires open reduction. The use of the Roger Anderson splint where it is available may in many instances obviate this necessity.

FRACTURES OF THE RADIUS AND ULNA

In dealing with a fracture of both bones *without displacement* one should exercise extreme caution not to convert a simple problem into a difficult and often serious one. Correct it gently. Avoid all possible turning of the arm in obtaining fluoroscopic views. The flexibility of the portable x-ray unit is of great aid in this regard, in fluoroscopy at reduction, and in obtaining radiographs for permanent records. In the case of displaced fractures of the radius and ulna, at whatever level the injury exists, two cardinal principles must be observed: (1) to restore the proper length and alignment of the radius, because upon this the function of the hand depends; (2) to establish and maintain the interosseous space. In the upper third the difficulty usually lies in maintaining the alignment, because the weight of the plaster bearing down at this point causes a posterior convexity. This can be overcome by applying a shoulder spica, thus carrying the weight of the plaster at the shoulder. In the middle third difficulty in maintaining the interosseous space is encountered by some, but in my experience cross union has never been seen. Bohler incorporates two short rods in his plaster, one on the dorsal and one on the volar aspect which he presses into the interosseous space. Roger Anderson has given us a very good method of skeletal traction. Length is the more important factor particularly in regard to the radius. If either fracture is transverse open

operation is not necessary. If both are oblique, either skeletal traction or open reduction may be necessary. If the latter is unavoidable, fixation of the radius is usually all that is required. It should be done early, to facilitate primary union and to obviate if possible the use of the heavy and non-absorbable forms of internal fixation, by accurate anatomical reposition of fragments. Sometimes a chromic ligature around the oblique fragments or through a drill hole is all that is required. The simplest form of fixation is always the best. Skeletal traction can be obtained by the use of the Kirschner wire combined with overhead suspension, flexing the elbow to 90°. The wire should be inserted proximal to the radio-ulnar articulation at the wrist. Fractures of the lower third are practically always transverse, and occur in children. Reduction is accomplished by complete pronation of the forearm, sharp angulation of the fragments with very firm pressure on the dorsal aspect of the distal fragment. Practically all of these can be reduced by this method.

These fractures, like all the foregoing, should be immobilized in a circular plaster lined with one layer of flannelette or stockingette, from the axilla to the metacarpal phalangeal joints, elbow flexed to 80°, supination at an angle which gives the best apposition and alignment of the fragments; fractures of the upper third, usually in full supination, while those of the lower and middle thirds are placed midway between full supination and pronation. This is maintained by applying the plaster around the hand leaving the fingers and thumb free. It should not extend on to the phalanges. This permits active movements of the fingers from the very beginning. If the patient is leaving hospital immediately this plaster should be split throughout its entire length to ensure satisfactory circulation in the event of swelling, and thus avoid a Volkmann's paralysis. (I offer no apology for mentioning these details because they are too often disregarded by some of the best surgeons).

This outline covers in a brief and superficial manner the methods of reduction and fixation of these fractures.

The fluoroscope should always be used to check positions before and after manipulations. If a flexible portable unit is not available two fixed tubes at right angles to each other are a good substitute. Radiographs should be taken

immediately following fixation and again in a few days, to determine how satisfactorily the position is being maintained.

Worthy of particular mention is the fact that active exercise of the fingers and thumb should be encouraged and obtained from the very beginning of treatment. Carrying the fingers in full extension without active movement has led in many cases to a permanent disability of a very disabling degree. If the hand can be used when the plaster is removed, function of the forearm will return much more quickly. The length of the period of fixation varies according to the age of the patient and the type of fracture. Fractures of the elbow joint should be immobilized for three weeks. Four weeks may be considered a minimum for a fracture of the shaft of the forearm in a child. Eight weeks is a minimum for both bones of the forearm in a patient of middle age. Longer periods can be employed without fear of disability if active movement of the hands is insisted upon from the beginning.

Non-union of the bones of the forearm results most frequently from (1) too short a period of fixation; (2) too early supination and pronation; (3) the use of early passive manipulation; (4) lack of reduction and inadequate fixation.

In conclusion, I would leave with you the thought that the forearm bears the same relation to the hand as the neck to the head. The bones of the forearm give the hand stability. By the muscles, blood vessels and nerves the hand obtains its nutrition and carries out its movements. It is upon the recovery of the functions of all these structures that the result of the treatment of the fracture of any forearm is judged.

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ANÆSTHESIA FROM THE PATIENT'S POINT OF VIEW*

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HOW often we have heard the remark, "It's not the operation I dread, doctor, but the anæsthetic!"

Many of us can remember personal impressions of the operating table where the anæsthetic seemed like a nightmare. In recent years such a change has come over our methods that there should no longer be any such experiences. The purpose of this paper is to bring to our attention as anæsthetists those factors and conditions which make for good anæsthesia from the patient's point of view. This aspect of our specialty is not new, and I have nothing original to report, so experienced anæsthetists must forgive me if I offer to young men who hope to make their living from anæsthesia some suggestions regarding their attitude toward the patient. My remarks are addressed particularly to those who have had their training in large public hospitals where often the patient has no more individuality than that of a name on the list of the work for the day. Personal contact between anæsthetist and patient should be fostered in order to promote confidence. A brief physical examination by the anæsthetist is usually advisable.

An interesting chapter could be written on the stethoscope in anæsthesia—not as an instrument for precise diagnosis but as a means of gaining the confidence of the patient. We know that in cases of doubtful cardiac function mere stethoscope examination is not sufficient to satisfy the requirements of scientific medicine, but in the average normal case there is nothing which gives more encouragement to the patient than to have the anæsthetist apply the stethoscope and then pass some such remark as "Well there's nothing wrong with your heart", or "That heart sounds as if it is good for another fifty years!" So, whether you hear anything or not, my advice is, use your stethoscope.

The choice of the anæsthetic and the method

to be used must depend on the nature of the operation and the condition of the patient, and, of course, the wishes of the surgeon should be taken into consideration. However, more and more surgeons who have confidence in their anæsthetists are leaving the choice to us. So anæsthetists must be prepared to exercise their own judgment in this matter. Our first consideration should, of course, be safety, but in most cases the preference of the patient may be consulted. From my own observation I have concluded that most patients prefer a general to a local anæsthetic, providing we can make general anæsthesia comparatively comfortable. At those hospitals with a reputation for good general anæsthesias we find a decreasing demand for local, regional and spinal methods. The introduction of avertin and the barbiturates, and the replacement of ether by cyclopropane and the other gases has entirely altered the patient's attitude toward general anæsthesia. Now many patients return for a second or third operation without any apprehension regarding the anæsthetic, knowing that they will go to sleep almost imperceptibly, and will wake up more or less comfortably without having to face days of nausea from ether saturation. My personal opinion is that local and spinal anæsthesia are almost always accompanied by a certain amount of nervous strain which may lead in a few cases to serious and persistent mental shock. In order to see what a patient feels like under spinal anæsthesia I did what many good anæsthetists have been afraid to do, had a spinal anæsthetic administered to myself for a herniotomy. I felt no pain and I was not really afraid, but even in the familiar surroundings of our own operating room, and in spite of nembutal and morphine, I was under considerable nervous tension, and my conclusion afterward was that it was an interesting but distinctly uncomfortable experience. Of course, if one gives very large doses of barbiturates and morphine and hyoscine so that the patient is really asleep before the spinal anæsthetic is ad-

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ministered the nervous tension is removed, but I cannot make myself believe that such polypharmacy is good for the patient. So we use spinal and local anaesthesia only when we believe these methods are specially indicated for a particular case, and I am an enthusiastic advocate of avertin or the barbiturates in moderate doses as a preliminary to gas anaesthesia. I prefer avertin to nembutal for abdominal operations because patients like it better, and I believe its effect is somewhat more predictable.

If the patient is to have avertin the anaesthetist should administer the injection himself, for although this requires no particular skill it is often the only time the patient sees the anaesthetist, and to the patient this injection is regarded as the anaesthetic, no matter what may be given to him later in the operating room. A patient pays a bill more cheerfully to a doctor he has seen than to one of whom he has no recollection!

When avertin is being given to a child I see no reason why the parents should not be allowed to remain in the room if they wish. It often gives a child confidence to have his mother beside him when a strange procedure is being undertaken, and it certainly gives the parents confidence in the anaesthetist to watch their child drop peacefully off to sleep. The more we can understand the ignorance and the fears of the laity, the more the public will respect our profession.

I am very much opposed to the practice of putting a patient on an uncomfortable stretcher half an hour before the time for operation and wheeling him in this embarrassing position through the corridors, only to wait in some ante-room until the omnipotent surgeon is ready to give him his attention. I believe the pre-operative order which is routine in some hospitals, of "hypo on stretcher", should be discarded. Preliminary hypnotic medication, whether it is to be avertin, nembutal, or morphine, or something else should be given in the patient's own room, and when the operating room is ready the patient taken there in his bed with as little commotion as possible.

Patients are sensitive about such things as false teeth and the state of their hair or complexion. If it keeps up their morale to come to the operating room with painted lips and

blackened eyelashes, I say, let them. They never know how bedraggled their faces may look after an hour or two of anaesthesia, and no harm is done. Many times I have removed a toupee or wig after the patient is asleep and carefully readjusted it to keep up the illusion before the patient awakes. Scrupulous care should be taken of religious medals, rosaries, and such good luck tokens as the patient may wish to take to the operating room. When rings do not actually interfere with the operative procedure I like to leave them on if the patient wishes, for who knows what sentimental values and what depths of emotion may be stored up in these little bits of gold. It is sometimes terrifying to have one's hands tied down before the anaesthesia begins, so I believe such preparation should be left until the patient is unconscious.

From the patient's point of view the induction is the most important period of anaesthesia, for it is then when lasting impressions are sustained. The use of avertin and the barbiturates has spoiled to some extent the "art" of anaesthesia, and yet with any patient who comes to the operating room in a conscious condition there is scope for the anaesthetist to display his skill during induction. When I started to give anaesthetics we had in our hospital only open ether, and there is no better way to learn the art of a smooth induction than to discard all the new paraphernalia of pleasant anaesthesia and to go back to the open ether mask. However, I do not let our interns do this, since I do not think it fair to our patients.

Quietness in the anaesthetizing room during the induction period is essential, but this fundamental principle is all too often forgotten by busy nurses and laughing, talking surgeons and interns. I believe that the anaesthetist should usually talk to the patient during the induction period. Even the most banal remarks sometimes give great comfort at this time, as I can remember in my personal experience. We, for whom the operating room is a means of livelihood, must never forget that for each patient the operation is a tremendous adventure, and that the moment above all others when the emotional upset may be greatest is just as consciousness is going. Don't let us ever get frivolous about our work in the sight or hearing of the patient.

Many patients have a dread of waking up before the operation is over. It is often wise

for the anæsthetist to explain that he is present throughout the operation and continues to administer the anæsthetic during that time according to the patient's requirements.

The conduct of anæsthesia during the operation is really the most important part of the anæsthetist's work, but since from the patient's point of view this period is all a blank, we will not discuss it in this paper. I just want to say, be careful with airways and mouth gags and suction tubes, for sore throats and lips and broken teeth are often misunderstood and resented.

The anæsthetist should visit all his patients before they leave the hospital. A discussion of incidents in connection with the anæsthetic will be appreciated by most patients, and forms a personal relationship between anæsthetist and patient which may be of value on some future occasion.

Obstetrics is a branch of medicine where the question of anæsthesia is of the greatest importance to the patient. A difficulty some of us have encountered in this field is the unwillingness of many obstetricians to avail themselves of an experienced anæsthetist's service. There are still a few obstetricians who seem to believe that pain during childbirth is a God-given accompaniment of this maternal ordeal, to be borne with fortitude, and good for the soul. When I see such a man standing beside a woman in labour I wish that some miracle might happen whereby he and his poor patient would change places. However, the principal reason for inadequate obstetrical anæsthesia is, I am sure, the economic argument. Patients are inclined to bargain so about the cost of confinement that the obstetrician is unwilling to add an anæsthetist's fee. The patient goes into labour without any provision having been made for anæsthesia, and at the last minute an intern is called to administer whatever he or the obstetrician may happen to know something about. The trouble with this arrangement is that really satisfactory obstetrical anæsthesia demands a higher degree of skill than almost anything we may be called upon to do in the operating room, and should be a matter for complete cooperation between obstetrician and experienced anæsthetist. I have observed that very few patients object to paying a reasonable fee to the anæsthetist who has really helped them through the terrifying ordeal of childbirth. Some obstetri-

cians, with whom I have the privilege of working, make a practice of explaining to the patient before she comes to the hospital that it will be to their mutual advantage to have a specialist administer the anæsthetic, and tell her that this will mean a small extra fee. The women are almost always grateful for this advance information regarding the importance of anæsthesia, and they make a point of asking for this service at subsequent confinements.

The method of obstetrical anæsthesia which I have found to be most successful for the average case is a combination of nembutal or heroin for the first stage, Sword's technique of nitrous oxide-air analgesia for the second stage, and cyclopropane for delivery and repair. During the nitrous oxide analgesia period the patient should remain awake and cooperative, and the anæsthetist then has an opportunity to exercise his knowledge of psychology by tactful encouragement. At this period patients particularly resent hearing doctors and nurses in the case room discussing the affairs of the day as if the ordeal of childbirth were not the most important subject in the world just at that moment. Many women have told us that all they remembered of their experience in the case room was that someone with a very kind voice was giving them encouragement.

It seems to me, therefore, that the anæsthetist, whose work touches so many aspects of the practice of medicine, is in a particularly favourable position to understand the patient's point of view. We can do much to bring this point of view to the attention of surgeons and hospital administrators. During the past generation many hospitals have been built around the surgeon as the all important element in the organization, and everything seems to have been designed primarily for his convenience. The motto which should be carried by every department of every hospital is that "This hospital exists for the benefit of the patient". The interests of nursing staff, of interns, of physicians, surgeons and anæsthetists are subsidiary to those of the patient. Conversely, what benefits the patients benefits us, and whatever we as anæsthetists can do to make the patient's stay in the hospital safe, comfortable, and pleasant will more than repay us for the thought and effort involved.

SULFANILAMIDE IN THE TREATMENT OF GONORRHOEA

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DURING the past three years in Europe and during the past year in America a considerable number of reports have been published attesting the value of para-amino-benzene-sulfonamide in the treatment of hæmolytic streptococcal infections.¹ More recently it has been shown that it is also a potent chemotherapeutic agent in meningococcal infections.² The close relationship between the meningococcus and the gonococcus led Dr. Perrin H. Long, who has been a pioneer in America in the study of sulfanilamide, to suggest that it be given a trial in gonorrhœa. The first report was made recently by Dees and Colston³ and their results were decidedly impressive. The purpose of this paper is to report the results in the sulfanilamide* (para-amino-benzene-sulfonamide) treatment of 134 patients with gonococcal infections of the genito-urinary tract treated in the Provincial Government Clinic, Edmonton.

THE MODE OF ACTION OF SULFANILAMIDE

Long and Bliss⁴ have shown that a 1:10,000 concentration of para-amino-benzene-sulfonamide in serum broth markedly inhibited the growth of alpha hæmolytic streptococci, gamma streptococci, pneumococcus types I and II, several varieties of Neisseria from the throat, *M. tetragenus*, *H. influenzae* and *H. hæmolyticus*. The growth of *S. aureus*, *B. typhosus*, *B. paratyphosus A*, *B. paratyphosus B*, enteritides, Flexner, Shiga and several other Gram-negative bacilli, was not affected by this concentration of the chemical. This inhibition may also occur *in vivo*, but in addition to this effect of the drug it is felt that the microorganism must also be damaged to permit of a marked degree of phagocytosis by the leucocytes. On the other hand the experiments of Mellon, Gross and Cooper⁵ showed no indication that phagocytosis is a

factor in the mechanism of the therapeutic action of this drug, and this seems to be borne out by the fact that the pustular discharge in acute gonorrhœal urethritis begins to diminish about four hours after the ingestion of large doses of sulfanilamide. The question of the mode of action is therefore unsettled.

Toxicity.—All of our 134 adult patients tolerated 80 grains of sulfanilamide daily for four days without ill effect. It is known that some patients have tolerated $\frac{3}{4}$ of a grain per pound of body weight daily for a month without serious results. Six of our patients developed skin rashes during the period of maximum dosage. In all six the eruption occurred after exposure to sunlight and was confined to the hands and face, there being sharp lines of demarcation at the rim of the collar and the bottom of the sleeves. In four of the patients the eruption was urticarial, in one a mixture of urticaria and dermatitis, and in one dermatitis only. The urticaria cleared up within twenty-four hours after discontinuing the drug and did not recur when the medication was resumed with half the former dosage.

All of our patients were conscious of a drug effect, which varied from a slight feeling of dizziness or lassitude to a definite inability to do work which required mental concentration. Headache, when it occurred, was not severe. There were no cases of acidosis and only two of fever (routine temperatures were not taken). One patient developed a condition suggestive of methæmoglobinæmia, which disappeared in a few hours when the drug was stopped and did not recur when treatment was resumed with a smaller dosage. Complete blood counts have been done on more than one hundred of our patients and no changes attributable to the treatment have been noted. The gastric analysis in 8 of our failures showed normal acidity. No renal changes were noted. It should be borne in mind however that in case of renal impairment retention of the drug in the blood occurs.

* The para-aminobenzene-sulfonamide used in this series of cases was supplied by the Winthrop Chemical Company, under the trade names of "Prontylin", and "Prontosil", and by the Lederle Laboratories ("Sulfanilamide").

In short it would appear from the study of the literature and from personal observation that sulfanilamide is relatively non-toxic.

Absorption and excretion.—Marshall, Emerson and Cutting⁶ have shown that in the dog absorption from the gastro-intestinal tract is rapid, being usually complete or nearly complete in four hours. In patients when large amounts of sulfanilamide are administered daily in divided doses nearly 100 per cent may be recovered from the urine when equilibrium between intake and output is established. It takes from two to three days to establish this equilibrium and the same time to free the body of the drug after it is discontinued. Subcutaneous injection of the substance does not lead to higher blood concentration than when it is given by mouth. It passes readily into the tissues and is found in the cerebrospinal fluid in only slightly less concentration than in the blood. The optimum concentration in the blood stream is 1:10,000 and this is easily obtained by rather large initial doses of the drug and is maintained by considerably smaller doses. A method for determining the blood level has been described by these authors⁶ and more recently a simpler and more sensitive modification has been described by Marshall.⁷ The human subject excretes the drug partly unchanged and partly conjugated in the form of an acetylated derivative.

CLINICAL OBSERVATIONS

Sulfanilamide treatment of 51 male patients was begun on May 15th, these being the ordinary clinic run of patients attending on that day, and no selection of patients was made. Some had resisted the ordinary clinic treatment for months, and the common complications of the disease were represented in this preliminary group, including 1 of acute prostatitis, 5 of chronic prostatitis, and 1 of epididymitis. From day to day additional cases were started on sulfanilamide, to bring the total of this series to 30 females and 104 males. The diagnosis of gonorrhoea was confirmed routinely in each case by the demonstration in the laboratory of typical intracellular diplococci in the methylene blue stained smear of the urethral discharge. In the females smears were also made from the cervix. This was checked by the independent examination of duplicate smears stained by Gram's method in the Provincial Laboratory.

Of the 30 female cases in this series all had positive smears within the five days preceding the institution of the sulfanilamide treatment. All the patients were ambulatory except one with acute prostatitis.

Of the males the first 51 of the series varied as to the duration of the disease from one day to several months; the succeeding 53 cases were all recently acquired infections of from one to five days' duration and coming under treatment for the first time. In the entire series of 134 adult cases the treatment consisted of: (1) 80 grains of sulfanilamide daily for the first four days; 40 grains daily for the second four days and 20 grains daily for the next seven days. The daily dose was divided into four equal portions and given every four hours from 8.00 a.m. to 8.00 p.m. (2) Each patient was instructed to drink large quantities of water and of milk; all other fluids were prohibited. Other than this no instructions were given as to diet. (3) No local treatment of any kind was administered to any of these patients. Other patients treated in the clinic but who disappeared before completing the course, even though they appeared to be cured, have not been included in this series.

The cured patients have been followed for periods varying from one month to more than three months subsequent to the conclusion of the treatment. Relapses have occurred up to three weeks following an apparent cure, and although re-infection could not be ruled out these cases have been listed with our failures. Five of our uncured patients were placed in hospital, and for a period of five days were given prontosil subcutaneously in doses of 10 c.c. every four hours, or a total of 250 c.c. for each patient. In four of them the disease was not influenced by the treatment; the fifth case was very much improved but not cured. Our determination of a cure in the male was based on the absence of gross pus or shreds in the first and second glasses of urine and by the demonstration of not more than eight pus cells per oil-immersion field in the prostatic fluid; in the female by a series of not less than ten negative daily smears from the urethra and cervix.

Of our total of 134 cases 87.3 per cent were cured. Of the 104 males 91, or 87.5 per cent, were cured, 6 in one day, 13 in two days, 25 in three days, 14 in four days, 8 in five days and

25 in six to fifteen days; of the 30 females 26, or 86.6 per cent, were cured, but it is difficult in the females to decide just when the cure was effected. The females were seen and smears were made daily, some for as long as two months. In all cured cases the smears became negative within two weeks and symptoms of the disease disappeared. Of the 17 failures in this series not one seemed to be influenced by the drug. No complications whatever occurred in any of our patients during treatment.

One should approach the task of evaluating the curative effect of a new drug with an attitude of scepticism. Too often brilliant therapeutic successes have in the end proved to be due to optimism on the part of the observer. Many more cases will have to be observed over longer periods of time before a final decision can be reached, but the preliminary results would seem to indicate that sulfanilamide is of outstanding merit in the treatment of gonococcal infections.

SUMMARY

1. Twenty-six, or 86.6 per cent, of 30 females and 91, or 87.5 per cent, of 104 males affected

with gonorrhoea were cured within fifteen days by a course of treatment consisting solely of the oral administration of sulfanilamide and large quantities of fluids.

2. No complications occurred in any of the patients in this series subsequent to the commencement of sulfanilamide therapy.

3. The total dosage of sulfanilamide given to each patient was 620 grains during a period of fifteen days.

4. The drug sensitizes some patients to sunlight, which produces an acute urticarial eruption on the exposed skin.

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AN UNUSUAL SEQUENCE OF EVENTS IN A GASTROJEJUNAL ULCER

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IN his comprehensive paper, "Jejunal and gastrojejunal ulceration following gastrojejunostomy" (1909), Paterson stated that the occurrence of secondary ulceration cast somewhat of a shadow over the results of an admirable operation. This statement is still true to some extent at the present time. However, when gastrojejunostomy is performed with full recognition of the indications for the operation now generally agreed upon the incidence of this complication is somewhat reduced. It is virtually impossible to arrive at a true estimate of the incidence of gastrojejunal ulceration. Wright,¹ reporting the "Collective Inquiry by the Fellows of the Association of Surgeons of Great Britain and Ireland", states that it is a fair estimate to say that secondary ulcer occurs in about 6 per cent of patients after posterior gastrojejunostomy for duodenal ulcer. It is still

more difficult to determine the incidence of acute perforation of a gastrojejunal ulcer. Toland and Thompson,² in a review of the literature, found 93 authentic reports of acute perforation, to which number they added 10 new cases. They suggest an incidence of slightly less than 1 per cent. Wright, according to his report, found 60 cases of perforation in a total of 458 cases, or an incidence of 13.1 per cent. These figures indicate the wide discrepancy in such estimates.

Hæmorrhage is a more common complication. It had complicated gastrojejunal ulcer in 14 of the 103 cases of acute perforation reviewed by Toland and Thompson. In Wright's series of cases of gastrojejunal ulcer hæmorrhage occurred in 124 patients and in 65 of these it was severe or repeated. We desire to describe a case of gastrojejunal ulcer which not only presented both these complications but a further

complication in the form of obstruction in the early post-operative period.

CASE REPORT

L.H., a carpenter, aged 56, was admitted to the Holy Cross Hospital, Calgary, on July 9, 1935, complaining of severe upper abdominal pain and weakness. Sixteen years before a posterior gastrojejunostomy had been performed for a simple ulcer of the duodenum. For about a month before admission he had noted occasional dizziness but no other symptom. Three days before, while downtown, he had become suddenly faint and came home and went to bed. He had one spasm of pain in the left hypochondrium, but this passed off in about an hour. The following day there were vertigo, weakness, rapid pulse and distant heart sounds. The following day an enema produced a large tarry stool. The blood count showed 2,300,000 red blood cells and the hæmoglobin 35 per cent. He vomited once, with normal stomach contents. There had obviously been a hæmorrhage from the upper bowel. On the day of admission, about 7.00 a.m., he was seized with severe upper abdominal pain which continued until 1.00 p.m., when he suddenly suffered terrific pain in the left abdomen below the umbilicus. On admission at 2.30 p.m. the temperature was 97.4° F.; pulse, 90; respirations 20. There was no rigidity or localizing tenderness in the abdomen. By 6.00 p.m. there was evidence of beginning peritonitis in the left lower abdominal quadrant and fluoroscopic examination of the abdomen showed free air in the abdominal cavity. The white blood count was 13,400, with 80 per cent polymorphonuclears. Operation was performed at 8.30 p.m. An acute perforation was found about the middle of the anastomotic area of the old gastrojejunostomy on the jejunal side, about 3 mm. in diameter, with a very small surrounding area of induration. The perforation was closed and a Penrose drain inserted beneath the omentum. A blood transfusion was given while the patient was on the table. The course was uneventful for ten days, during which period the patient had a further transfusion and was started on milk by mouth.

On July 19th he had two large hæmorrhages from the stomach, of 23 and 12 ounces. The red blood count at this time was 3,100,000 and the hæmoglobin 45 per cent. The pulse rose to 120. The patient reacted very well; fluids were started again, and by July 25th he was doing well on a regular Sippy regimen. On July 26th he began to have cramp-like abdominal pains and profuse vomiting. A roentgen-ray plate of the abdomen showed dilated loops of small bowel. Treatment was instituted for incomplete obstruction, with Wangenstein suction and continuous intravenous drip. Enemata gave returns of flatus only. By July 31st it was apparent that conservative treatment was inadequate and laparotomy was performed. An obstruction was located in the upper ileum, the bowel being occluded by a band of adhesions. The obstruction was liberated. From this time on his course was uneventful. He was placed on the usual Sippy management and was discharged on August 13th, thirty-five days after admission. After one year and eight months the patient remains clinically well.

COMMENTS

This case presents several points of interest.

(1) The sequence of complications — hæmorrhage, perforation, hæmorrhage and obstruction

—is unusual in gastrojejunal ulceration. (2) The gastrojejunal ulcer, manifesting itself first by hæmorrhage and shortly afterwards by perforation, occurred 16 years after the original operation. In their review, Toland and Thompson found that the interval between the performance of gastrojejunostomy and the acute perforation of gastrojejunal ulcer varied from 5 days to 18 years. In only 16 per cent of the cases perforation occurred from 5 to 18 years after operation. (3) The acute perforation of a gastrojejunal ulcer was preceded by no prodromal symptom beyond slight bleeding producing some vertigo, followed by massive hæmorrhage. The site of the pain in the acute perforation in this case was in the left lower quadrant of the abdomen, and on examination the maximal tenderness and rigidity were found to be in the same area. These findings are characteristic, and are due to the fact that the fluid escaping from the perforation passes downward to the left of the vertebral column beneath the omentum. (5) The site of the secondary ulcer in this case was about the middle of the anastomotic area. In the majority of cases gastrojejunal ulcer is anastomotic. Wright, in his review, found 285 anastomotic ulcers as against 99 jejunal ulcers. (6) The interval between the time of perforation and operation in the present instance was 8 hours. The operation consisted of simple suture with drainage. Even under these conditions the prognosis is grave. Wright reported a mortality of 23 per cent, and Toland and Thompson in 114 acute perforations found 34 deaths, a mortality of 29.8 per cent.

The patient's course since the operation has been most satisfactory. Careful dietetic management has been followed, and further operative measures have not been necessary.

Since this case we have had another of acute perforation of a gastrojejunal ulcer which terminated fatally. This patient was not seen until more than 24 hours after the ulcer perforated.

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THE ADRENAL CORTICAL HORMONE: A METHOD OF ASSAY AND OF PREPARATION*

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THE difficulties and differences of experience that are so marked in the literature of the past five years on the adrenal cortical hormone are gradually resolving themselves. The failure to attain, even after 6 years, general corroboration of a medical discovery of the magnitude of that reported by Swingle and Pfiffner in 1931 is surely unique. Even as we write it remains true that no laboratory has confirmed the findings of Swingle and Pfiffner⁶ with anything approaching the conclusiveness of their evidence, and this despite the fact that these authors furnished apparently adequate details for the preparation of their extract and the treatment with it of adrenalectomized animals.

The early clinical reports on the use of Swingle and Pfiffner extracts were convincing. A number of patients suffering from Addison's disease were treated with beneficial results by extracts prepared in this department. One patient already described by Cantor and Scott^{1, 2} was kept alive for over two and a half years, during which time relapse was induced by withdrawal of hormone and remission was attained by restoring it on 11 separate occasions. The diagnosis in this patient was confirmed at autopsy. During most of this time, when free from colds or intercurrent disturbances, the patient was adequately maintained on about 2.0 mg. per day of rather crude hormone preparation, the equivalent of about 50 g. ox adrenal gland. Our experience with patients suffering from Addison's disease was thus similar to, for example, that of Rowntree and Snell.³

Our difficulties began with the use of animals adrenalectomized for assay purposes. During the winter of 1932-33 we adrenalectomized 56 cats by the two-stage operation. In no case, after removal of the second gland, were we suc-

cessful in maintaining the weight of the animal, with daily doses following the operation equivalent to as much as 500 g. adrenal gland. In certain instances the administration of extract was followed by a raised body temperature and relief of weakness. Our animals commonly developed wound infections, abscesses, and, notably, respiratory infections, including pneumonia. Today we place little weight on our experiences with adrenalectomized cats, but they are perhaps worthy of record alongside the similar findings, *e.g.*, of Cleghorn⁴ and of Rogoff.⁵

On trying to reconcile these experiences with those of Swingle and Pfiffner⁶ a number of considerations now emerge that appear to make this possible. In the first place the importance of salt intake for the adrenalectomized animal was not realized in this early period. Swingle and Pfiffner⁶, it is true, described a dietary regimen for their cats consisting of canned salmon 5 days a week, with raw liver or kidney for the remaining two days, but it is clear from the context of their paper that they did not realize that such a ration was peculiarly suited to their animals on the ground specifically of its relatively high NaCl content, which would be ingested voluntarily to a maximum from the eagerness with which cats eat salmon. For, although it was clear from the much earlier work of Baumann and Kurland⁷ and Marine and Baumann⁸ that in the adrenalectomized cat the blood Na and Cl are significantly reduced, the K raised, and further that the administration of "practically all sodium salts used prolonged life", nevertheless the importance of these observations was not realized until Loeb⁹ showed that the chemical blood picture in 3 cases of Addison's disease was essentially similar to that of the adrenalectomized cat. Loeb *et al.*¹⁰ and Harrop *et al.*¹¹ showed that in the adrenalectomized animal there was loss of Na

* One of us (M.M.C.) is indebted to the Banting Research Foundation for a personal grant during the years 1932 to 1934 for assistance in the prosecution of the research work reported in this paper.

and water in the urine, and suggested that a main function of the cortical hormone was the preservation of electrolyte and water balance in the body. Meanwhile Rubin and Krick¹² seem to have been the first to confirm the life-prolonging effect of Na salts as first observed by Marine and Baumann in adrenalectomized animals. Finally Loeb¹³ reported the successful treatment with NaCl of a patient with Addison's disease.

Since 1933 these fundamental observations have been amply confirmed and greatly extended. Harrop *et al.*¹⁴ were able to maintain bilaterally adrenalectomized dogs apparently in normal condition over prolonged periods, up to 5 months, without the use of any adrenal gland extract but by the administration, sometimes parenterally, of NaCl and NaHCO₃. Withdrawal of the salts soon induced typical adrenal insufficiency. Similar results have recently been reported by Nilson.¹⁵

As a diagnostic test for Addison's disease Harrop, Weinstein, Soffer and Trescher¹⁶ suggested the use of a salt-free diet. Loeb, Atchley and Stahl¹⁷ note the consistent and sometimes alarming results of such withdrawal of salt from the diet of the patient with Addison's disease. The same authors record the successful treatment of 16 cases of this disease over long periods by high salt diets and without recourse to extracts. The whole trend of research on the subject indeed forces one to the surprising conclusion that the adrenalectomized animal or the patient with Addison's disease may be maintained indefinitely in apparently good health without adrenal hormone but merely by the administration of salts adequate in amount and balance. Such a conclusion in no way minimizes the importance of the adrenal cortical hormone.

The work of Darrow and Yannet,¹⁸ of Gilman,¹⁹ and especially of Swingle and his colleagues in a series of recent papers in the *American Journal of Physiology*, has added greatly to our understanding of the main function of the adrenal cortical hormone. In essence this function is the regulation of salt and water distribution in the organism. The animal with adrenal insufficiency is suffering primarily from loss of extracellular water including that of the blood plasma. We thus get the typical signs of dehydration, and from loss of water from the blood plasma we get hæmoconcentration, a greatly reduced blood volume,

and, mainly for that reason, a reduction of blood pressure to the death level in untreated cases. Darrow and Yannet, by intraperitoneal injection of isotonic glucose followed by paracentesis, were able to reduce greatly the Na and Cl of the blood plasma and thereby produce a picture similar to that in adrenal insufficiency. They showed clearly in dogs, monkeys and rabbits that the hæmoconcentration was induced without loss of fluid in the urine, but simply by a shift of extra- to intra-cellular water. The condition of shock thus produced is dramatically relieved by intravenous injection of saline to replace that removed in the ascitic fluid. Swingle, Parkins and Taylor²⁰ showed that the adrenalectomized dog similarly depleted of plasma electrolyte could not withstand a certain slight degree of hæmorrhage which the dog with intact adrenals always recovered from. The same workers, with Hays,²¹ then describe perhaps the most remarkable demonstration of the function of the adrenal hormone. They allowed dogs to develop severe adrenal insufficiency with very low serum Na and Cl, and by completely withholding food or giving a "salt-free" diet they were able to revive the animals by the administration of massive doses of hormone, without a rise in the blood Na or Cl. They were able to maintain such animals active and apparently normal for a period of three weeks, when salt was again given. They attribute the absence of symptoms and the reduction of hæmoconcentration and blood urea to normal to the effect of the cortical hormone on the shift of tissue fluids to the extracellular spaces and blood stream. The intimate relation of the water and salt balance of the organism to the condition of "shock", from, *e.g.*, surgical operation, trauma, and hæmorrhage, has been so convincingly shown by Swingle and his associates that one is tempted to think of the adrenal glands as the main "shock absorbers" of the organism.

The mechanism of action of the hormone is still far from clear. It is apparent that the dehydration signs in adrenal insufficiency are accounted for, not by loss of water as urine but almost solely by shift of extracellular water into the cells. Sodium, we might expect to follow the water into the cells, but as analytical evidence still seems to be lacking on this point and the general belief at present is that Na is confined to extracellular fluids and K to intra-

cellular, it would be rash to argue for such a possibility. A loss of Na in the urine has been observed in Addison's disease and in animals going into insufficiency. Whether or not this loss is sufficient to account for all the Na lost by the body's extracellular water, it would seem to establish the cardinal point that deficient cortical function means the loss of the power of the body to conserve Na (and perhaps other electrolytes). By salt medication alone it is possible to replace this Na, but only through the use of excessive amounts of salt to meet the great wastage which takes place in absence of the cortical hormone. It would appear to be still a moot point as to whether the hormone specifically acts on the special cells of the kidney normally responsible for reabsorption of Na from the glomerular filtrate, or whether its influence is in alteration of extrarenal cell permeability. It would at least appear highly improbable that the azotæmia associated with cortical insufficiency can be accounted for on grounds of renal insufficiency as we understand it in nephritis.

It has been mentioned that the plasma K increases in adrenal insufficiency. By injection of K salts it is possible to produce a clinical picture in animals similar to that in adrenal insufficiency (Zwemer and Truszkowski²²). A small intake of K has become as important as a large intake of Na in the treatment of patients with Addison's disease (Wilder *et al.*²³).

EXPERIMENTAL

The work reported here had as its primary objective the chemical isolation of the adrenal cortical hormone. Through circumstances alluded to above we failed with cats to find a satisfactory assay animal for extracts which we had excellent clinical evidence for believing were active. We then adopted the suggestion of Kutz²⁴ of using month-old adrenalectomized rats. Our immediate problem became twofold: (A) the development of a satisfactory assay method for (B) extracts prepared by different procedures from adrenal glands. We will take each of those aspects of the problem separately.

A. THE RAT METHOD OF ASSAY

Our rat colony is of pure Wistar strain and inbreeding has been deliberately avoided. After weaning the rats are maintained on the basal ration of

Whole wheat meal	456 parts
Whole milk powder	200 "
Linseed meal	96 "
Casein	30 "
Alfalfa meal	12 "
Cod liver oil	25 "

intimately mixed and fed as dry meal. After operation the animals are given distilled water and no supplementary food of any kind is allowed. In certain of our early experiments a dried biscuit of the above materials, along with which were incorporated meat scraps, etc., was made for use over Sundays only, but this was discontinued on finding that controls given this ration exclusively showed a smaller weight loss and longer survival than rats on the strict basal ration (*v.* Table II Group N). A study of Table I will make clear our method of assay. The rats here included were bilaterally adrenalectomized by double incision under ether and the following morning sorted into groups of 5 and placed in 6 cages. They were listed by number in sheets specially printed for the purpose and identified by sex and the necessary ear-marks. Their weights were recorded and they were given their first dose of extract. The extract was given once daily for 9 days in all, and the rats were weighed daily until death. Of the 30 rats recorded it will be observed that 4 were alive and gaining weight 7 days after treatment was stopped. For reasons which will be discussed such rats are excluded from the results. In each group the initial and final weights and the survival days were summed up and the conclusions from each group arrived at as stated in the Table.

The results in Table I can be approximately assessed by comparison with the summary results of the control Groups A, B, and D of Table II. Here we have 109 strict control rats and 511 virtual controls of an age comparable with that of the rats detailed in Table I. The extract used in Table I is still regarded as exhibiting activity in a 5 g. dose because of the 2-day extension of the control survival period, despite the marked weight loss shown. Groups C and E of Table II serve to demonstrate the longer survival period of larger rats.

The effect of active extracts on month-old rats is shown in Groups F and H, and on older rats in Group G of Table II. The large Groups D, F and H have been compiled from our records which include tests on a great variety

TABLE I.

Rat Lot No. 334 CAGE NOS. 13-14		EXTRACT No. 184 DOSE 0.5 c.c. 20 g. GLAND																Survival days
Days post-operative		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
1. —	F	39	40	40	42	42	43	45	46	46	48	47	44	D	13.0
2. R.	F	57	58	56	57	58	59	58	57	58	60	58	D	12.0
3. LR.	F	57	58	59	60	61	62	62	62	62	62	62	58	D	13.0
4. L.	F	56	57	54	54	54	54	54	52	50	D	10.0
5. RR.	F	55	57	58	59	61	64	69	70	75	77	82	82	84	87	90	92	Liver
6. —	M	56	56	59	62	66	70	74	76	77	83	88	92	93	96	100	110	Liver
7. L.	M	56	56	57	58	60	62	64	62	60	61	D	11.0
8. RR.	M	53	55	54	55	57	60	60	62	62	65	64	D	12.0
9. R.	M	50	51	50	50	50	50	50	51	49	51	D	11.0
10. LR.	M	53	53	51	51	52	51	51	50	49	48	D	11.0
Totals — 421 g. (initial)		434 g. (final)																93.0 days
Hence, 8 rats, average weight 53 g., gained 1.6 g. in average survival period of 11.6 days.																		

CAGE NOS. 15-12		EXTRACT No. 184 DOSE 0.5 c.c. 10 g. GLAND																Survival days
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
1. St.	F	55	54	54	54	55	56	55	55	57	57	55	D	12.0
2. —	F	55	55	55	55	56	58	58	58	59	61	59	D	12.0
3. L.	F	55	56	55	55	56	57	55	55	D	9.0
4. R.	F	50	51	51	53	55	56	61	61	65	68	72	69	74	72	75	77	Liver
5. LR.	F	48	49	49	49	49	48	48	46	47D	9.5
6. —	M	48	49	48	49	49	51	51	49	48	50	D	11.0
7. L.	M	57	58	55	55	55	55	55	53	50D	9.5
8. R.	M	53	53	51	51	50	50	49	D	8.0
9. RR.	M	56	55	54	55	55	56	54	52	50	D	10.0
10. LR.	M	56	56	57	59	61	63	64	64	64	66	65	D	12.0
Totals — 483 g. (initial)		477 g. (final)																93.0 days
Hence, 9 rats, average weight 54 g., lost 0.7 g. in average survival period of 10.3 days.																		

CAGE NOS. 11-10		EXTRACT No. 184 DOSE 0.5 c.c. 5.0 g. GLAND																Survival days
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
1. —	F	46	46	46	45	45	43	42	41	D	9.0
2. R.	F	47	48	46	46	46	45	43	D	8.0
3. LR.	F	45	45	44	44	43	43	42	D	8.0
4. —	M	59	59	58	58	55	52	50	D	8.0
5. R.	M	49	50	50	50	50	47	45	D	8.0
6. —	M	51	53	52	51	49	46	D	7.0
7. L.	M	54	54	51	52	50	50	48	46	D	9.0
8. LR.	M	59	59	56	55	53	52	D	7.0
9. RR.	M	48	49	48	47	46	46	D	7.0
10. R.	M	51	54	57	59	63	65	72	77	83	90	97	104	97	105	..	112	Liver
Totals — 458 g. (initial)		411 g. (final)																71.0 days
Hence, 9 rats, average weight 51 g., lost 5.3 g. in average survival period of 7.9 days.																		

Note.—F=female. M=male. Other letters are ear-marks.

TABLE II.

Ration	Group	Number of rats	Average weight g.	Average gain (+) or loss (-) at death g.	Average survival in days	Remarks
Basal	A	34	55	-2.4	5.5	Strict controls.
"	B	75	65	-5.0	5.2	
"	C	49	82	-7.1	6.9	
"	D	511	61	-4.3	6.0	Virtual controls treated with inactive but non-toxic extracts.
"	E	222	86	-9.5	6.8	
"	F	485	61	-2.6	8.5	
"	G	192	81	-6.0	10.6	Extracts showing some activity. Very active extracts.
"	H	312	58	+3.4	10.6	
Basal +5% NaCl	K	13	71	+5.0	12.0	
Basal +10% butter	L	8	69	+0.5	7.4	
Basal +fresh meat	M	10	75	+0.6	8.1	
Basal +meat scrap	N	9	73	-1.5	7.2	

of material obtained from our gland fractionation processes. In many such fractions we did not expect activity but wanted to leave no possible loop-hole of escape of potent material, hence the large number of rats in Group D. Group F includes rats treated with extracts showing activity but not maintenance, while Group H demonstrates both maintenance of weight and potency to keep the rats alive.

The remaining small groups of rats, K, L, M and N, listed in Table II, serve to show the marked influence of certain supplements to the basal ration.

DISCUSSION OF THE RAT ASSAY METHOD CONTROL RATS—

"Livers".—The chief early objection to the use of the adrenalectomized rat as an assay object for the cortical hormone, that is the high proportion of animals indefinitely surviving the operation, seems, by improvement in technique, to have been quite removed. The operation is as fatal to the rat as to animals of other species, though it has been claimed that certain strains of rat show a greater proportion of survivors than other strains. From 2,304 animals we found 207 lived indefinitely. That is about 9 per cent of "livers". Over certain periods when operations have been frequent and the operator "in practice", we have noticed that, *e.g.*, in a consecutive series of some 250 rats the "livers" were only about 2 per cent. But we usually expect to have to eliminate one rat in each lot of 10. Of the 30 rats in Table I it may be observed that 4 have been eliminated from the records as they were still gaining weight 7 days after extract treatment had been stopped. We have detected no sex difference either in the number of "livers" or in the duration of survival after operation. About 1 per cent of our animals died within two days of the operation, presumably from hæmorrhage or cause other than adrenal insufficiency. These, as well as the occasional rats we observe with pneumonia, are also excluded.

Survival periods and weight changes of controls.—In our month-old rats the average survival period of controls is about 5.5 days, with a weight loss of 2.5 to 5.0 g. Schultz²⁵ in 77 month-old rats found 100 per cent mortality and an average survival of 5.7 days, with no weight change. Cartland and Kuizenga²⁶ found only 5 "livers" in 192 month-old rats,

and a survival period of 6.88 days, with no mention of weight changes. The ration of the rats of the latter workers contained about 1.3 per cent NaCl, as compared with about 0.4 per cent fed by Schultzer and ourselves.

Age or weight of rats.—Uniformity of weight of controls and test animals has been regarded as important by all who have worked with rats. The longer survival period of our larger rats is in accordance with the findings of most other workers. All obvious advantages are in favour of the use of 50 to 60 g. rats for test purposes.

Ration.—In our experience the most important factor in control and test adrenalectomized rats is the ration, especially in regard to the NaCl it contains. The reasons for this are perhaps apparent from our introductory remarks. The effect as shown in Group K, Table II, of the addition of 5 per cent NaCl to our basal ration is at first sight so startling as to call in question the whole assay method. Whether there are factors other than NaCl in the other supplements given to rat Groups L, M and N, Table II, which alter the control picture, is a subject which needs investigation. It does not affect our present discussion, apart from emphasizing the cardinal necessity for strict dietary control in all animals used for cortical hormone assay. On this point Schultzer has recently shown that the daily administration of 9 mg. NaCl, as isotonic saline, prolongs the survival period 2 days, and the same amount twice daily, by 3.6 days, as compared with like-weight rats receiving no injections. We have made similar observations with our own rats.

ASSAY RATS—

Time interval of test.—Kutz,²⁴ who first used the month-old adrenalectomized rat as test object, administered the hormone for 20 days after the operation, and assessed the potency of his extract by the proportion of animals surviving at the end of that time. This procedure has been followed by Schultzer and by Cartland and Kuizenga. Our own routine, as described above, has been to give extract for 9 days. The only argument we can see that may be raised against this procedure is that an occasional control rat will live for 9 days without treatment. The expectancy of life in the rat adequately treated for 9 days is about twice that of controls, which appears to us to provide a safe enough margin. Our fairly extensive ex-

perience has assured us of its reliability. The saving in both time and material is valuable.

Survival period and weight change.—In assessing the value of an extract we use the two criteria of survival period and weight change. The former of these we regard as the more fundamental and reliable. This is also the view of most workers, though Grollman and Firor²⁷ suggest a rat unit based on the amount of extract that will permit normal growth in 40 to 50 g. rats.

The picture as presented in Table I is typical of our findings with regard to the two factors of survival period and weight change. In order of decreasing dose the lots lived 11.6, 10.3 and 7.9 days and showed weight changes in the same order of +1.6, -0.7 and -5.3 g. Were we disposed to speak in terms of rat units we should say that the 10 g. dose contained about 1 rat unit, as the life expectancy was nearly reached and the rats nearly maintained their weight with this dose. The 5 g. dose is inadequate on both counts though it still exhibits activity on the evidence that the survival period has been extended 2 days. The 20 g. dose, which we regard as double the maintenance dose, has much less effect in prolonging the survival period and increasing growth than we might expect. With our best extracts we rarely find the period of survival to exceed 13 days and the greatest weight increase we have obtained was 13.8 g. in a survival period of 12 days. Unoperated on 50 g. rats on our basal ration gain about 40 g. in 12 days, so that our best growth on treated adrenalectomized animals represents only about one-third of the normal weight increase. With the great majority of our assays the weight increase does not exceed 10 per cent of normal in cases, as in Table I, where the survival period is satisfactory. Yet we find in general, as in Table I, a relationship between survival period and weight change. This same relationship is seen to hold in the large Groups F and H, and indeed also G, of Table II.

Schultzer and Cartland and Kuizenga report consistently greater gains in their treated animals than we get in ours, yet rarely exceeding one-third of the growth rate of their unoperated on controls. Schultzer is inclined to the conclusion that the rate of growth during the injection period is independent of the dose, and

like Cartland and Kuizenga takes little account of weight change in the assay of an extract. We have no fault to find with this attitude as we do not yet know if the adrenal glands are necessary for growth or not. There are perhaps few who believe that the "salt-and-water" hormone, as it has been called, is likely to have any influence on growth, but most of us have rather been working on the assumption, that with adequate administration of the salt-and-water hormone the factors normally responsible for growth are allowed to proceed unimpeded. Our own experience, with that of the others mentioned above, would now appear to call this assumption in question. We are of the opinion that adequate evidence is still lacking to prove that normal growth is attainable in the adrenalectomized animal. It may prove possible, with the best hormone preparations we now have at our disposal, along with a ration suitably supplemented with minerals, to obtain normal growth, but until this has been accomplished it is perhaps better to maintain a mind open to the possibility that many of our adrenal extracts may contain besides the salt-and-water hormone variable amounts of a specific factor influencing growth. And it should be mentioned, in qualification of our general finding noted above, that with different extracts, rather than with different dose levels of one extract, we have sometimes found weight changes which were not explainable by differences in the potency of the extracts to keep the rats alive. Some evidence for this statement may be found in Table III.

"Units" of hormone.—There is as yet no generally accepted unit to express the potency of the cortical hormone. It is also obvious that, e.g., a "dog unit" or a "rat unit" will depend on the diet of the animals during assay, and "units" determined on the same species in different laboratories may differ widely. On the relationship of a dog unit as determined by Pfiffner, Swingle and Vars²⁹ with a rat unit defined by themselves, Cartland and Kuizenga²⁸ have provided us with important information. According to these workers 1 rat unit is equivalent to about 22 dog units, or on an equal weight basis to over 300 dog units. Through the courtesy of Dr. Cartland we have tested one of his extracts by our method and find that our rat unit tentatively suggested above

approximates to his, although our criteria are different. On the basis of the de Fremery test on rats Reichstein²⁰ observed that the hormone requirement for the rat was apparently much higher than for the dog. And from our own early experience with the patient W.B. mentioned in the introduction to this paper it appeared that a dose of hormone about 10 times the amount required to maintain a 50 g. adrenalectomized rat was sufficient to maintain this approximately 50 kg. man, suggesting that on an equal weight basis the rat required 100 times as much hormone as the human being. Evidence for great difference in species requirement is thus not wanting, but is as yet very inadequate. It is clear, however, that we need not expect the adrenalectomized rat to respond definitely to extracts providing less than about 20 dog units per day. We have for a long time felt that our many early disappointments in the response of adrenalectomized rats to different hormone preparations were due primarily to their containing insufficient of the active material.

On the best ration for assay animals.—From our remarks on the ration of control animals it may be observed that the parenteral administration of NaCl with the extract may affect the assay picture. It has never been our practice to give extracts in saline but always in distilled water with about 3 per cent alcohol. The fact that Schultzer, and Cartland and Kuizenga give their hormone in isotonic saline we believe may account for the better weight maintenance of their rats.

As stated earlier, the life of adrenalectomized animals can be greatly prolonged by giving them large quantities of salt. The lower the salt intake, the shorter the survival period of controls, and the less responsive we expect rats to be to hormone treatment. The question of the best level of NaCl in the ration thus arises, and it appears to us that an answer to this question has to be found and adopted before we can get comparable assay units for the cortical hormone. We do not pretend to have answered the question here beyond having chosen the lowest NaCl intake that we could conveniently get for our rats. Reasons for altering this level may emerge with further work. We consider that our conditions of assay are decidedly adverse to ready responses. Whether such condi-

tions unduly decrease the responsiveness of the adrenalectomized rat to hormone treatment is a question that awaits further investigation, but they at least add to our confidence in the potency of extracts which definitely overcome the adverse demands of the assay.

B. PREPARATION OF EXTRACTS

It would be futile for us to describe the many methods and modifications of methods we have used in our attempts to fractionate the cortical hormone from the exceedingly complex chemical mixtures yielded by adrenal glands. On the basis of our experience with about 1,000 kg. glands, processed usually in batches of 5 to 10 kg., we have developed a method which is relatively simple and reproducible and gives a maximum yield of hormone free from toxic materials. Its potency has been repeatedly proved in cases of Addison's disease and in adrenalectomized rats. The method, on the basis of 10 kg. glands, follows.

Method of preparation of concentrate of cortical hormone.—Ten kg. frozen adrenal glands are finely minced into 25 l. acetone to which 60 ml. 10N. H_2SO_4 are added. The mixture is warmed in a water bath and refluxed for 30 minutes: it is cooled to room temperature, poured through cheesecloth, and the residue expressed with a porcelain filter press. The residue is discarded. The expressed fluid is cooled to 4°, then filtered through paper in large gravity funnels into 12 l. balloon flasks. The filtrate is concentrated *in vacuo* to a volume of 5 l. This aqueous residue is cooled to 4°, and gravity filtered to obtain a perfected clear solution. The strongly acid solution is brought to faint acidity by the addition of NaOH. The solution is then concentrated *in vacuo* to a volume of 250 ml., the thin syrup poured into a 6 l. Erlenmeyer flask with washings totalling 250 ml. Five l. of acetone are added, the mixture is vigorously shaken and placed in the refrigerator for separation of the aqueous layer and the cold acetone supernatant fluid is filtered through a dry paper and the filtrate concentrated *in vacuo* to a volume of 50 ml. This, along with 50 ml. wash water, is poured into 500 ml. benzene in a separatory funnel. The mixture is shaken vigorously, allowed to separate, and the benzene layer transferred to a 4 l. flask. The aqueous layer is washed five times with 500 ml. of benzene for each washing. The combined benzene washings, about 3 l., are cooled to 6° and filtered through a dry paper. The filtrate is evaporated *in vacuo* to remove all the benzene leaving a thick brownish gummy residue. It is covered with dry cold acetone and soaked for some hours. The acetone is poured off and the process repeated until the acetone extract is colourless. The combined acetone washings are evaporated *in vacuo* to a small volume, transferred to a tarred basin, and dried *in vacuo* in a desiccator over H_2SO_4 in presence of sticks of NaOH. Weight of residue, 0.4 to 0.5 g. from 10 kg. of glands. The dried residue is now washed into a small cylinder with a definite volume of absolute ethyl alcohol (10 ml.) and stored in a refrigerator. It is usually entirely soluble, though a small flocculent brown precipitate may settle on keeping in the refrigerator. At this stage the material is practically free

from adrenalin, is non-toxic, and suitable for biological test when suspended in a suitable volume of water. The material is referred to at this stage as the "whole extract". More than half this material is biologically inactive as can be demonstrated by the subsequent fractionation procedure as follows.

The above alcoholic solution is filtered into a small wide-mouthed flask and brought to dryness in a vacuum desiccator. Absolute ethyl ether free from alcohol is poured over the dry residue, the flask stoppered and kept for some hours. The ether solution is filtered into a similar flask, and the residue re-extracted several times with ether. The well washed residue is biologically inactive. The combined ether extracts are dried in a vacuum desiccator and the weight of the residue recorded. Dry petroleum ether (b.p. 40 to 60°) is now poured over the dry oil residue. Under the petroleum ether the residue becomes friable. The fluid is separated and the solid washed several times with petroleum ether. The flask containing the residue is returned to the desiccator, the combined petroleum ether washings are kept in a stoppered flask overnight at 4°, when a little more solid separates. This solid, well washed with small amounts of petroleum ether, is added to the main residue which is the biologically active fraction.

To illustrate this fractionation, "whole extract" prepared as above and combined under gland lots 173 to 182, (Table III), and comprising 123.8 kg. glands, may be used.

"Whole extract" (acetone and
absol. alcohol soluble) ... 5.890 g. or 47.5 mg./kg.
Ether soluble 4.905 g.
Petroleum ether soluble 2.722 g. (by difference)
Petroleum ether insoluble 2.183 g. or 17.6 mg./kg.
The yield of active material ("petroleum ether insoluble") from other similar gland lots has usually been found to be from 15 to 20 mg./kg. of glands. The final dry material appears as a thick brown oil, very soluble in absolute ethyl alcohol, in which it is stored as a 10 to 20 per cent solution.

DISCUSSION OF PREPARATION

The method of preparation above described offers two main advantages over the usual Swingle and Pfiffner³¹ procedure: (a) it eliminates the very laborious distribution between aqueous alcohol and petrol ether which at best, according to Reichstein,³⁰ leads to an appreciable loss of active material, and (b) it gets rid of adrenaline without the use of permutite and indeed without any special departure from the direct course. The use of acetone instead of alcohol for the first treatment of the glands was indicated by the acetone stage described in the first communication of Swingle and Pfiffner. The solution was acidified and refluxed at this stage first on the suggestion of Grollman and Firor.²⁷ The short period of refluxing appears to do little more than bring the acetone into contact with the tissue, an action enhanced perhaps by the acid. A more important reason for the presence of the acid at this stage lies in the fact that it renders filterable the aqueous residue after distillation of the acetone. In neutral solution the suspended material is in a

colloidal condition. If the insoluble material at this stage is not removed difficulties are encountered later in the benzene separation and the final "whole extract" contains much more inactive material and is likely to be toxic to animals. As the active constituent of the glands appears to be slightly soluble in water, and though it may be much more soluble in the complex aqueous solution at this stage, filtration is carried out with the relatively large volume of 5 l. on the above basis of starting material. As the substance separated is soluble in acetone the latter must be completely removed from the aqueous residue for the filtration to have its maximum advantage.

Apart from the greater fire hazard attached to the use of large quantities of acetone it has the disadvantage that it gives rise to an intractable foam in the course of the vacuum distillation. This is much lessened by cooling the first expressed fluid before the filtration preceding distillation.

On neutralizing the acid aqueous filtrate above mentioned there is no appearance of precipitate, and indeed the solution remains clear during the subsequent distillation to a syrup.

The second treatment with acetone serves to remove inert material comprised of inorganic salts, phospholipids, and much adrenaline. In the next stage a relatively large volume of benzene is used for washing the aqueous residue, as evidence from assays indicates that the last traces of active material are very difficult to remove from the aqueous layer by benzene washings. Cooling the benzene before filtration leads to the removal of the maximum amount of water from the benzene phase, so that the acetone next used to dissolve the hormone remains nearly absolute.

As has been noted, the "whole extract" is practically free from epinephrine. It yet contains certain inert material soluble in petroleum ether. Before removing this material however the ethyl ether soluble fraction is obtained from the "whole extract". Much pigment and nearly 20 per cent of inert material insoluble in ethyl ether, but soluble in acetone and absolute alcohol, are thus removed. Subsequently, practically a clean separation is effected between the petroleum ether soluble material and the biologically active material which is insoluble in petroleum ether but soluble in the other absolute solvents used. It is important that the solvents

be used in the order mentioned, as it has been shown from assays, that much, or indeed all, of the active constituent is transferred to the petrol ether phase if applied in the early stages of the preparation.

The above method differs from those already published on the preparation of the adrenal hormone notably in the use of absolute solvents in a definite order. According to the principles adopted there is little likelihood of appreciable loss of active material at any stage and many assays of discarded fractions support this assumption. More conclusive evidence on the same point indeed lies in the fact that the active dose of the hormone on the basis of original gland equivalent is as low on our final petroleum

combined batch 122-172 shows marked potency with a dose of 0.10 mg. of the same fraction. The fractionation of batches 173-182 proves the same point, but indicates that a slight activity is present in the ether insoluble part of the whole extract, although the rats used to test this fraction were larger than desirable. On this point, however, from other evidence, we believe that the hormone is only sparingly soluble in alcohol-free ethyl ether, but it goes readily into the ether phase in the above fractionation largely because the material soluble in petrol ether is still present.

The dated assays in Table III show a loss of activity of the material on keeping in absolute alcohol in a refrigerator. The loss was appar-

TABLE III.

Extract No.	Dose mg.	Dose gland equivalent g.	Rat Lot No.	Number of rats in lot	Average initial weight g.	Gain (+) or loss (-) at death g.	Average survival days	Remarks
165-172	0.40	10	258	7	61	-2.3	11.1	Whole extract.
" "	0.38	10	259	6	69	-2.3	10.8	Ether sol.
" "	0.16	10	260	5	64	+3.8	12.6	" " , petrol ether insol.
" "	0.50	20	259a	6	69	-9.0	6.8	" " " " sol.
122-172	0.10	10	284	7	63	+5.7	13.6	" " " " insol.
173-174	0.49	10	264	5	56	+6.4	11.4	Whole extract.
175-176	0.58	10	265	5	83	+0.2	14.4	" "
177A	0.47	10	266	4	52	+6.5	10.0	" " , immediate extraction
177B	0.65	10	267	5	60	+5.6	12.2	" " delayed extraction.
178A	0.47	10	268	6	62	+4.3	10.8	" " " "
178B	0.34	10	269	4	62	+7.2	12.2	" " immediate "
179-180	0.41	10	279	6	59	+2.0	11.5	" "
181-182	0.53	10	280	6	63	+0.7	11.2	" "
173-182	0.16	10	282	10	56	+10.5	12.5	Ether sol.: P.E. insol. (Jan., 1936)
" "	0.66	30	283	7	54	-6.2	6.8	" " " sol.
" "	0.17	30	285	9	81	-5.0	11.0	Ether insol., alc. sol.
" "	0.16	10	296	9	60	+5.1	10.8	Ether sol.: P.E. insol. (May, 1936).
" "	0.32	20	301	4	52	+13.8	12.0	" " " " (Aug., 1936).
" "	0.16	10	320	12	47	-2.8	6.5	" " " " (Jan., 1937).
" "	0.32	20	321	10	48	-3.5	7.3	" " " " " "

ether insoluble fraction, as on any earlier fraction in the preparation.

ASSAY OF EXTRACTS AND FRACTIONS—

In Table III are presented typical assays on a series of "whole extracts" prepared as described above, and in doses equivalent to 10 g. of gland. The survival periods are consistently good, but the weight changes somewhat variable. Extract No. 165-172, fractionated according to the procedure described above, is shown to contain the hormone in its ether soluble fraction, and to contain little, if any, in its fraction soluble in petroleum ether. The

ently not great during the first 8 months but was very marked by the end of a year.

FURTHER OBSERVATIONS ON PREPARATIONS AND ASSAYS

In the first extracts made by the Swingle and Pfiffner method it was observed that the dried residues were not entirely soluble in absolute ethanol. The insoluble material was mainly NaCl. When ethyl ether was added to the alcoholic solution a copious white precipitate was always obtained. This could be obtained crystalline by re-solution in alcohol and re-precipitation with ether. It was found to be

inactive on the patient W.B. of Cantor and Scott, and was not investigated further. At least half of the organic matter of such extracts was made up of this material insoluble in ether-alcohol mixtures. When acetone was used instead of alcohol for the extraction of the glands this material was no longer present in the final extracts.

The essential difficulty of the preparation lies in the separation of the hormone without appreciable loss from the large amounts and great variety of lipids present in the gland material. On this separation also depends the removal of epinephrine from the hormone fraction. In an attempt to overcome this difficulty we extracted the alcoholic extract of the glands, adjusted to about 70 per cent alcohol concentration, directly with petroleum ether, and proceeded as usual with the aqueous alcohol fraction. The final extract, on a 15 g. dose level, proved to have very little activity. We concluded that the bulk of the hormone had been removed with the fat by the petrol ether. This single experiment may have been misleading as Cartland and Kuizenga²⁸ have obtained good results by a rather similar device.

We have obtained definite evidence of prolongation of the survival period, usually with great weight losses, from hot aqueous extracts of the glands.

The hormone does not rapidly disappear from frozen glands, as we have prepared good extracts from glands frozen for 6 to 8 months. Glands collected separately from steers and cows yielded extracts of about the same potency.

The solubility of the hormone in water gets less as purification proceeds. We have spent much time in trying to utilize its property of slight solubility in water. We have shaken it with many changes of water for many hours and find the residue, taken up in a small amount of alcohol and suspended in water, still shows marked activity. The fraction soluble in water, if again dried and re-extracted, behaves as the original. This is a fact of some importance when preparing the hormone for patients. For administration to rats we merely add an aliquot of our alcoholic stock solution

to a suitable volume of sterile water, and administer the generally slightly cloudy resulting solution. Increasing the amount of alcohol of course clears the solution, but it has been our practice to keep the alcohol below 3 per cent. For patients the solution is made in a like manner, and then the cloudiness cleared by the addition of a small amount of a dilute Na_2CO_3 solution. The material is quite soluble at pH 7.4. The solution is then Seitz-filtered with little loss. We have no reason to believe that the hormone is more soluble in isotonic saline than in distilled water.

The object of this paper has been merely to give evidence for the reliability of a rat assay method, and, this established, to prove by it the soundness of a method of preparation of active concentrates of the cortical hormone. The material under Extract Nos. 122-172 and 173-182 listed in Table III contained only a trace of N (0.04 per cent), a trace of P, and about 2 per cent ash; it was practically entirely free from epinephrine. It was not tested in doses lower than those listed in Table III, where in the case of No. 122-172, 0.1 mg. of material, representing 10 g. glands, showed marked activity, a finding which, compared with those of other workers, gives us much assurance that there can be little loss of active material in our fractionation procedure.

SUMMARY AND CONCLUSIONS

1. A method of assay for the adrenal cortical hormone, based on the use of the month-old adrenalectomized rat, has been discussed and approved, from experience with over two thousand animals.
2. The need for a recognized strict dietary regimen for assay animals is regarded as fundamental to the establishment of any useful quantitative expression of assay.
3. A method of preparation of concentrates of the adrenal cortical hormone has been elaborated from the study of many batches of glands, in sum about 1,000 kg.
4. The final biologically active fraction, which is practically free from N, will maintain adrenalectomized rats in daily doses of 0.1 mg., equivalent to 10 g. whole ox adrenal gland.

An extensive bibliography consulted for this paper is included in reprints and may be had on application to the author.

Case Reports

A CASE OF TERMINAL ILEITIS

By V. F. ONHAUSER, M.D.

Winnipeg

Terminal ileitis is not a new disease. In 1932 Crohn first described the condition as a clinical entity. At various medical centres series of cases have been reported, thus increasing the fund of knowledge. The terminology varies with different authors—terminal ileitis, chronic cicatrizing ileitis, regional ileitis. Each name emphasizes some outstanding characteristic either in the site or pathology of the lesion. In the differential diagnosis, Mixter says, we must consider ileocaecal tuberculosis, ulcerative colitis, lymphosarcoma, actinomycosis, and carcinoma. In the case here reported, which had atypical features, we gave serious consideration to the possibility of typhoid, para-typhoid, and brucellosis.

Judging from the cases reported, the symptoms, the onset, and the course of the disease vary widely. With the acute onset there is sharp colicky abdominal pain in the right lower quad-

rant coupled with fever and a moderate leucocytosis. A mass may be palpable. The symptoms may closely simulate appendicitis. A high percentage has this pre-operative diagnosis.

Crohn describes four main types of the clinical course:—(1) acute intra-abdominal disease with peritoneal irritation, as above described; (2) symptoms of ulcerative colitis; (3) symptoms of chronic obstruction of the small intestine; (4) persistent and intractable fistulae in the right iliac fossa.

CASE REPORT

E.S., male, single, aged 24, first presented himself at my office on February 5, 1937.

His chief complaints were: hæmorrhoids and constipation of 3 to 4 years' duration, with weakness, lassitude, and anorexia for 6 months. The hæmorrhoids were not painful and bled occasionally in small amounts. There was a feeling of anal fullness and of incomplete evacuation. During the past winter the patient felt "generally tough and run down". He also had lost considerable weight, estimated at about 30 pounds. Later on the patient's mother gave one additional piece of history which I consider significant. She said the patient would suddenly cover his face and complain of a sharp abdominal pain. This was of only momentary duration, and he was able to continue his meal or carry on a conversation. These attacks came mostly at mealtime. The patient slept well, and had no headaches.

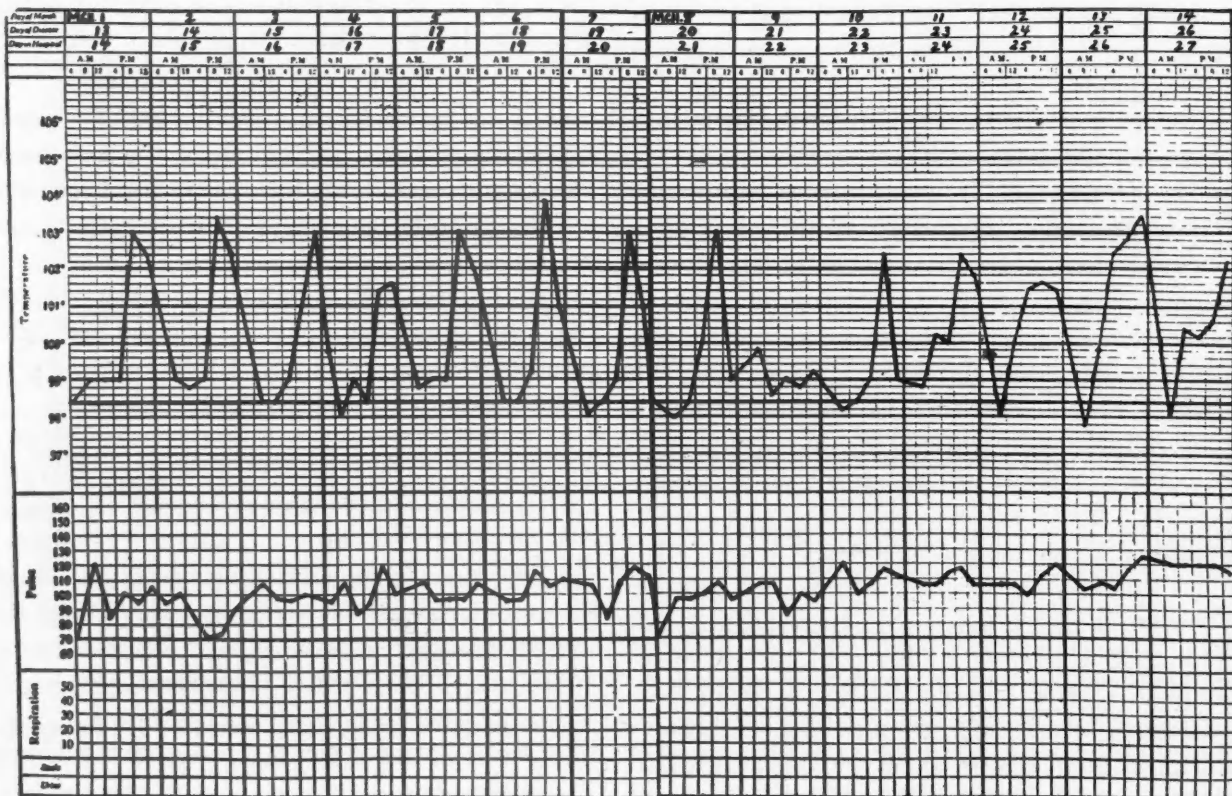


Fig. 1

There was no pain or cough, but some expectoration in the morning. There was no dyspnoea or oedema.

Previous illnesses.—Jaundice—3 years ago, (sick three weeks).

Family history.—There was no history of tuberculosis or chronic cough. The family were all well. The patient was Canadian by birth and had never lived in the tropics. The family milk supply was from a recognized dairy that supplies a large part of this city.

Physical examination revealed an intelligent and alert young man. There was marked emaciation and anæmic pallor of the skin and buccal and conjunctival membranes. Pulse, 108; temperature, 98° F.; blood pressure, 70/110. Cardiac examination was negative.

The abdomen was soft and negative to palpation; no point of tenderness and no masses were made out. Haemorrhoids, grade 3 plus, externo-internal type, with a small amount of erosion, were present. The sigmoidoscope, passed 9 inches, showed nothing abnormal except the anæmic pallor already noted in the mucous membranes of other parts. There was no dysuria and no nocturia. Urinalysis was negative.

My diagnosis at this time was externo-internal haemorrhoids with a marked secondary anæmia, and operation was advised.

On February 8th the patient was admitted to hospital and prepared for operation. That night his temperature rose to 101.6° F., with a pulse of 100 to 110, and normal respiration. Leucocyte count, 13,900. Influenza was prevalent at the time, and in view of this the operation was cancelled and the patient advised to take a week's rest in bed. In spite of the above findings the patient declared he felt no different than usual.

A week later, February 15th, the patient again presented himself at the office. He said that he had not been actually ill during that period but felt the benefit of a week's bed-care and rest. He was readmitted to the hospital the same day and was prepared for operation the next morning. On admission he had a temperature of 99° F., and during the night it reached 101° F. The pulse and respirations remained constant at 100 and 20, respectively. At this time I felt satisfied that we were not dealing with an acute febrile condition such as influenza, and proceeded with the operation under 50 mg. of novocaine, given as a low spinal. A ligature and excision haemorrhoidectomy was done.

At no time was there any untoward local condition following the operation, except that healing was somewhat slow. But this was not any more than could be accounted for by the anæmia and the persistent diarrhoea that developed after the operation.

During the greater part of his hospitalization (see Fig. 1) he had an elevation of temperature at 8 or 12 p.m. reaching 102 to 104° F., and then subsiding to 99° F. and normal. The pulse was 100 to 120; respirations, 20. The curious thing was that he was never aware of these sharp elevations of temperature. At morning rounds he would greet us with a smile and declare that he had had a fair night. When this unusual type of temperature continued we realized we were confronted with some unusual condition.

The following laboratory tests were made. Tuberculin (1-1,000)—negative. Repeated sputum examinations for tubercle bacilli, negative. X-ray of chest (February 24th, and March 16th) negative for tuberculosis. Diaphragm normal. The heart and great blood vessels shadows were normal; the lung fields clear. Physical examination of chest, by Dr. D. L. Scott of the Central Tuberculosis Clinic, was negative. Widal tests and para-typhoid, 1-80, were repeatedly negative. Stool examinations for blood, typhoid, amœbæ and other parasites were repeatedly negative. No tubercle bacilli were found in the stools.

Blood cultures: two were taken and reported negative after five weeks. *Br. abortus* skin test was negative;

the agglutination test was positive several times at 1-100. One strain of *Br. abortus* gave a negative reaction. The blood Wassermann and blood smears for malaria were negative. Blood count: red blood cells, 3,260,000; hgb., 53; colour index 0.80.

February 26th.—White blood cells, 26,800; polymorphonuclears, 76 per cent; small lymphocytes, 24 per cent.

March 1st.—White blood cells, 10,600.

March 6th.—White blood cells, 11,400; polymorphonuclears, 77 per cent; small lymphocytes, 20 per cent; monocytes, 3 per cent.

March 24th.—White blood cells, 26,450.

Intravenous pyelogram: the pelvis and calyces of the kidney were well visualized and appeared normal. The urine was clear, acid, 1.030, negative for albumin and sugar. Numerous microscopic examinations of the urine were negative for pus or red blood cells.

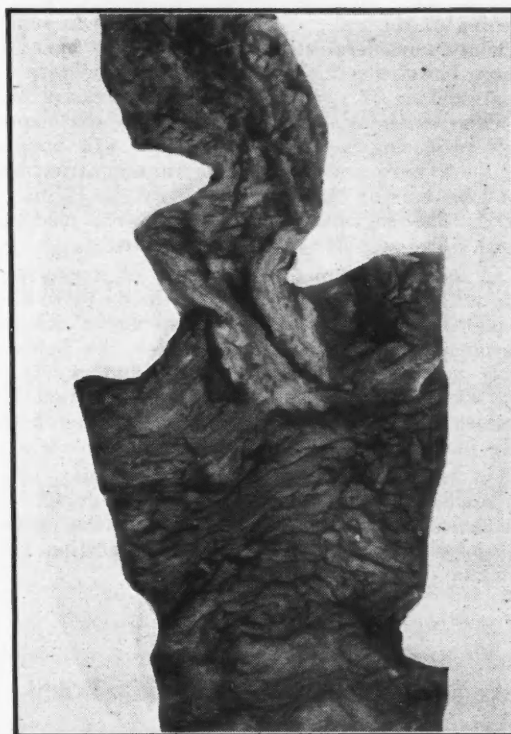


Fig. 2

The only positive finding was the agglutination for undulant fever.

In consultation Cadham did not think the symptoms were characteristic of undulant fever. He stated that undulant fever is extremely rare in Manitoba and he had never seen a proved case in the province. He also stated that on the examination of specimens of blood from local persons who had never experienced the clinical symptoms of undulant fever, a considerable percentage of the specimens gave a positive agglutination for *Br. melitensis*.

Foshay, of Cincinnati, kindly supplied us with brucellosis anti-serum. This was given in 30 c.c. doses intravenously at twelve-hour intervals for four doses, starting March 15th. The patient had been carefully tested for anaphylaxis. March 19th, the 4 p.m. temperature peak was 101.6° F. and the temperature continued to drop the next day. However our raised hopes were short lived, and on March 21st, the temperature again reached 103° F. I personally felt that, considering the critical condition of the patient, a dogmatic view was not tenable, and the serum treatment was justified.

On March 23rd, the patient suddenly experienced severe pain in the left lower abdomen with board-like rigidity, clammy sweats—a typical picture of an acute abdomen. His condition was too critical for a laparotomy. Death occurred on March 25th. Dr. Sara Meltzer performed the autopsy and records the findings as follows.

Post-mortem examination.—The body was that of a very emaciated young man. Significant findings were confined to the intestinal tract. The peritoneal cavity showed a generalized recent peritonitis with a partially walled off cavity in the pelvis filled with thin faecal matter. In the right lower abdomen the adhesions were old and the bowel wall very friable. On separating the dense adhesions, multiple perforations and fistulae were found in the lower ileum and caecum. The bowel lesion was confined sharply to the lower 12 inches of the ileum, the caecum, and lower third of ascending colon (see Fig. 2). In this portion of bowel there was thickening of the wall, which in the ileum was sufficient to produce considerable narrowing of the lumen. In the large bowel the thickening was only moderate. The mucosal surface of ileum showed very extensive ulceration with remaining intervening patches of heaped-up mucosa producing a lattice-like effect. In the large bowel there were scattered ulcers running transversely to the long axis of the bowel. Several ulcers had perforated. The regional lymph nodes were moderately enlarged. The rest of the bowel was normal.

The microscopic picture was that of a non-specific chronic inflammation, the cells being chiefly plasma cells, eosinophils, lymphocytes, macrophages and a few polymorphonuclears. In the small bowel the wall was diffusely involved and the ulcers deep and undermined. In the large bowel the inflammation was patchy with intervening areas of normal bowel. Here again there was the same striking undermining of the mucosa.

This is a hypertrophic, ulcerative lesion of the bowel, resembling ulcerative colitis, but occurring higher in the bowel, with the chief lesion in the terminal ileum, and should be classed with the condition known as terminal ileitis.

SUMMARY

1. A case of regional or terminal ileitis is reported.
2. Until near the end there was a striking absence of abdominal symptoms, apart from the persistent loose stools.
3. The case came to autopsy undiagnosed, all laboratory methods failing to explain (a) the persistent high fever; (b) the persistent liquid stools. Prior to hospitalization, patient had complained of chronic constipation.
4. By the irony of fate we saw no indication to use the only laboratory aid that might have given a diagnosis, namely, a barium series.
5. The symptoms of terminal ileitis were not as clear-cut or striking as some of the reported cases would lead us to believe.

My thanks are due the members of the attending staff of Winnipeg General Hospital, and to Dr. Lee Foshay, for their willing and kindly cooperation.

A CASE OF ARRESTED GROWTH APPARENTLY STIMULATED BY THE USE OF "ANTUITRIN GROWTH"

By K. A. BAIRD, M.D., C.M.

West Saint John, N.B.

A boy of sixteen years and three months was brought to me in October, 1935, by his mother, who said he had not grown at all for three years. She stated he was 9 lbs. at birth, had always been healthy, had had measles, chicken-pox and mumps about the age of five, at which time his growth had seemed to slow up considerably.

On October 22, 1935, the x-ray report on his right wrist and knee was as follows. "The epiphyses shown are far from being united. They show considerably less union than one would expect at this age period". The patient's measurements at this time and at various intervals during treatment are shown below.

He was given "antuitrin growth" (P. D. & Co.), said to contain 10 rat-growth units per c.c., averaging about two doses per week of 2 or 2.5 c.c. This was continued with one or two rest intervals until July 16, 1936, by which time he had received a total dosage of 160 c.c. During some of this time he was given thyroid by mouth.

Date	Height	Weight	Span, finger tip to finger tip	Chest girth at inspiration and expiration
1935				
Oct. 15	4 ft. 11½ in.	90 lbs.	5 ft. 1¼ in.	30¼ in.-28 in.
Nov. 29	5 ft.	95 lbs.
Dec. 31	5 ft. 1/8 in.	5 ft. 2 in.
1936				
Jan. 3	5 ft. 1½ in.	5 ft. 2¾ in.
Mar. 14	5 ft. ¾ in.	103 lbs.	5 ft. 3¼ in.
June 6	5 ft. 1½ in.
July 16	5 ft. 1 7/8 in.	105 lbs.	5 ft. 4 5/8 in.	31 1/2 in.-29 in.
	Antuitrin growth stopped			
Sept. 17	5 ft. 2½ in.
Nov. 24	5 ft. 2 7/8 in.	5 ft. 5 3/8 in.
1937				
May 10	5 ft. 4 in.	108½ lbs.	5 ft. 6¾ in.	31 1/2 in.-29 in.

On August 4, 1936, the following x-ray report was obtained. "The epiphyses at the distal ends of the right radius and ulna are larger and show more union than at the previous examination. . . . At the present time the epiphyses show somewhat less union with the diaphyses than is usual at the patient's age, but the development and union of epiphyses are normally subject to considerable variation."

A sister of the patient is slightly over a year older than he is. She has remained around five feet in height. X-ray shows her epiphyses practically completely closed, with nothing abnormal. Several other members of the family are apparently normal as to growth.

The dosage of antuitrin growth (P. D. & Co.) recommended is 6 to 10 c.c. per week. In this case the total never exceeded 5 c.c. per week.

COMMENT

In this case of delayed or arrested growth the patient's sister acts in part as a control. The giving of antuitrin growth (with some small doses of thyroid), in doses smaller than usually

recommended seems to have stimulated a growth process which continued for at least ten months after treatment was discontinued.

I wish to acknowledge the kind cooperation of Dr. E. A. Petrie in making the x-ray examinations and giving the reports quoted above.

Editorial

THE CONTRIBUTION OF CANADIANS TOWARDS THE SOLVING OF SILICOSIS PROBLEMS

SILICOSIS is a very live subject today. It is attracting the attention as a medical problem of research workers, and, as an industrial problem, of mine owners, mine executives and mining engineers. Naturally, the subject bulks most largely in those countries in which quarrying and mining are important industries. Accordingly, much good work has emanated from South Africa, Great Britain, the United States and Canada. Apart from the question of the cure of silicosis, which seems to be still remote, study has been directed to its incidence, pathogenesis, clinical features, its relation to tuberculosis, and the very practical matter of its prevention. Most of the Canadian studies have been made by workers in the Banting Institute of Toronto University, under the general direction of Sir Frederick Banting, with the expert collaboration of mining engineers, mine executives, geologists, and field operators in the mining districts of Ontario. The quality of the papers turned out goes to show the value of team-work in which experienced professional men, both medical and non-medical, have joined forces. As a result new facts have emerged and old positions have been consolidated.

The histological picture in the lungs of silicotics has been well worked out by Irwin,¹ Robson, Irwin and King,² Fallon and Banting,³ and Fallon.⁴

The incineration method of demonstrating silica in the tissues, used extensively by Policard, Cowdry, Scott, Schultz-Brauns, Scheid, and others, has been improved by Irwin (*loc. cit.*) who used strong hydrochloric acid to remove the non-siliceous moiety from the incinerated matter.

Belt, Irwin and King⁵ have studied silicon and dust deposits in the tissues of persons who had not been exposed to such dust in the course of their occupations. They found that silica was rather commonly present in the human body under ordinary conditions, but, of course, more abundant in the silicotic.

Fallon⁴ offers an explanation for the similarity in structure of the lesions of silicosis and tuberculosis and for their dissimilarity in behaviour. "It is evident from the work of Sabin and others that either the phospholipids of the tubercle bacillus alone or in combination with the lipoids of numbers of disintegrated monocytes produce the typical pathological lesions of tuberculosis. Early typical lesions of tuberculosis will disappear when the process is checked. This is not the case in the lesions of silicosis. The difference is probably due to the fact that when the tubercle bacilli are all destroyed the toxic phospholipids are gradually phagocytosed and removed, with the later removal of the scar tissue. In silicosis the monocytes become loaded with quartz particles; there is a physico-chemical change in the monocyte that causes disintegration of the cell and discharge of its contents; the liberated silica, which is practically unchanged, can now stimulate a further monocytic response, with further disintegration, and so on indefinitely. The extent of the

1. IRWIN, D. A.: The histological demonstration of siliceous material by microincineration, *Canad. M. Ass. J.*, 1934, **31**: 135; *ibid.*, Microincineration as an aid in the diagnosis of silicosis, *Canad. M. Ass. J.*, 1934, **31**: 140.
2. ROBSON, W. D., IRWIN, D. A. AND KING, E. J.: Experimental silicosis, quartz, sericite, and irritating gases, *Canad. M. Ass. J.*, 1934, **31**: 237.
3. FALLON, J. T. AND BANTING, F. G.: Cellular reaction to silica, *Canad. M. Ass. J.*, 1935, **33**: 404.
4. FALLON, J. T.: Specific tissue reaction to phospholipids, etc., *Canad. M. Ass. J.*, 1937, **36**: 223.

5. BELT, T. H., IRWIN, D. A. AND KING, E. J.: Silicon and dust deposits in the tissues of persons without occupational exposure to silicosis, *Canad. M. Ass. J.*, 1936, **34**: 125.

reaction depends upon the amount of inhaled silica which is imprisoned in the lung."

Franks⁶ describes an apparatus for removing dust in mines, based on the principle of electric precipitation as originally described by Lodge and later developed by Cottrell, which has been adapted, under the auspices of the Ontario Mining Association, for use when blasting operations are in progress. While not perfect, this machine has made it possible to remove much of the dust in mines, and no doubt, is a valuable aid in the prevention of silicosis.

It has long been suspected that irritating gases present in the air of gold mines may play a part in the silicotic process. Robson, Irwin and King² have put this idea to the test of experiment. The noxious gases found in gold mines consist mainly of oxides of nitrogen formed by the explosion of dynamite, together with smaller quantities of hydrogen, methane and carbon monoxide. Sulphurous gases occur also as a result of blasting sulphide-containing rock. These authors found that the addition of NO₂ and SO₂ to the atmosphere of dust breathed by their experimental animals appeared definitely to lower their resistance to pulmonary infection. The exposure of rabbits to siliceous dust combined with these (diluted) irritating gases gave rise, in periods of thirteen weeks or more, to an acute pulmonary silicosis characterized by typical siliceous fibrotic nodules. It should be added that their experiments did not support Jones's contention that silicosis is due to sericite rather than to particles of quartz.

While the literature on the subject of silicosis is now considerable, papers dealing with the clinical phases of the condition are relatively few. Therefore the contribution of Moore and Kelly,⁷ which embodies a most elaborate and searching study of the condition from the clinical and laboratory points of view, assumes special importance. These authors report the results of their investigation of 203 men working in one of the large gold mines of Ontario. The data collected in regard to each individual included age, particular occupation, period of exposure to dust, and a complete physical

examination. Red, white, differential and Arneth blood counts, hæmoglobin estimations, the blood sedimentation rate, urine and sputum analyses, cultures from the nose, throat, gums sputum, blood and urine, determination of the basal metabolic rate, electrocardiograms, and x-ray examinations of the chest were routine; blood analysis tests included determination of non-protein nitrogen, CO₂ combining power, urea, uric acid, sugar, calcium, phosphorus, cholesterol, and soluble silica; Wassermann and van den Bergh tests were made. No relevant matter seems to have been overlooked. Certain important conclusions emerge. Silicotics and those with far advanced fibrotic lesions differ from those not so affected in that they presented a lowered basal metabolic rate and a slowed pulse. In view of these observations it may be possible to recognize the miner who will likely develop silicosis before the appearance of the ordinary signs. The blood sedimentation rate was consistently higher in silicotics than in other groups. This may also have some diagnostic significance. The authors make the interesting observation that in some cases where thyroid medication did not raise the metabolic rate and where this actually dropped lower clinical improvement took place. The place of thyroid medication in dealing with silicotics deserves further investigation.

The recent work of Denny, Robson and Irwin⁸ is also worthy of special note, as it breaks entirely new ground. It has already attracted much attention in the special technical journals devoted to mining.

It is generally accepted that siliceous matter causes fibrosis of the lung only after it has passed into solution in the body fluids. Studies, therefore, on the solubility of various minerals may throw considerable light on their individual capacity for causing fibrosis. It is now well known that alkali increases the solubility of silica, as has been proved by the fact that cases of rapidly progressive silicosis have been induced by exposure to dust containing free alkali and a siliceous powder. The new work in Canada shows that the solubility of quartz *in vitro* is increased by the addition of carbonates and

6. FRANKS, W. R.: Silica dust, *Canad. M. Ass. J.*, 1934, **31**: 245.

7. MOORE, H. H. AND KELLY, J.: A clinical study of silicosis, *Canad. M. Ass. J.*, 1937, **36**: 339.

8. DENNY, J. G., ROBSON, W. D. AND IRWIN, D. A.: The prevention of silicosis by metallic aluminum, *Canad. M. Ass. J.*, 1937, **37**: 1.

hydroxides of magnesium sodium, potassium and calcium. Obviously, these or similar substances if present in quartz-containing rock may be expected to exert, with the silica, an important effect on the tissues of the lung. Conversely, and this is of the greatest importance, Denny, Robson and Irwin have discovered a way to reduce the solubility of silica. If quartz dust is mixed with aluminum dust of the same order of particle size, the proportion of aluminum in the mixture being less than 1 per cent, the dust produces practically no fibrosis in the lungs of rabbits, such reaction as there is being of the type found when relatively innocuous dusts are present in the lung. *Per contra*, the dust cells in the control group of animals treated with quartz dust alone showed the degeneration, giant-cell formation and elongation to become fixed-tissue cells, with migration into the pulmonary lymphatics which are so typical of ordinary silicosis. It was found also that *in vitro* the presence of small amounts of metallic aluminum dust almost completely inhibits the

solubility of siliceous matter. The authors state that they are not in a position to explain how metallic aluminum reduces the solubility of silica, but studies have been initiated on this problem. There is much more in this article that is worthy of attention than is given in this bald abstract. The experimental work was done under conditions designed to reproduce the dust-contaminated air of the mine after blasting.

It is, of course, too early to appraise the full value of these observations, but in the case of so insidious, intractable and damaging a condition as silicosis any ray of hope is welcome, and it may well be, as an outcome of this work of Messrs. Denny, Robson and Irwin, that, in addition to the measure of ventilation, it may be found possible to modify the dust of the mines so as to render it less likely to set up silicosis; or, possibly, a way may be found to treat the miner, to render him less susceptible, or even to cure him. A good step forward at least has been taken.

A.G.N.

RECENT CANCER RESEARCH

THE report of the Director of the Imperial Cancer Research Fund (Dr. W. E. Gye), 1936, is before us and is an important document. The subject is discussed under three main headings—carcinogenesis, viruses and radiotherapy.

Carcinogenesis.—Among the influences which can incite cancer are physical agents—x-rays, radium and ultra-violet light; chemical ones such as arsenic, aniline, complex hydrocarbons, tars and dyes; and gross animal parasites. Some of the chemical compounds are of especial interest since they are related structurally to the sterols which occur naturally in the body, as, for example, cholesterol. The bile acids are formed from these sterols and a product obtained from one of the bile acids, deoxycholic acid, and named methyl-cholantrene, when painted on mice produces cancer more quickly than any substance known. Here then is a material formed from substances always present in the body which is carcinogenic, and hence the conception has arisen that cells when placed under abnormal conditions produce

abnormal derivatives of sterols which are carcinogenic. Some of the naturally occurring hormones, as œstrin, are closely related chemically to the carcinogenic hydrocarbons, and so it is not altogether surprising to find that œstrin when injected subcutaneously over a period of months in mice will lead to the development of mammary cancer, even in male mice. Curiously, painting on the skin did not produce local cancer, but mammary cancer. This experiment demonstrates very clearly that a substance can be carcinogenic for one organ and not for another and also the importance of susceptibility in the genesis of cancer. It is stressed however that no fear should be attached to the use of œstrogenic hormones in practice, since large doses over a long period of time are necessary to obtain these results. Certain inbred strains of mice are known to be more susceptible to mammary cancer than a mixed strain, and an interesting experiment is reported in which animals of each group were tarred on the skin. Contrary to what might have been expected, there was no

higher incidence of cancer in the one than the other, showing that there is no support for the belief that there is a general susceptibility to the same carcinogenic agent; in other words, the remote cause of cancer is not always the same. As all malignant cells have the same fundamental biological properties one may assume that the intracellular change is the same, *i.e.*, from the point of view of proximate cause, cancer is a single disease.

Viruses.—Studies with the Shope rabbit virus papilloma have shown that the original benign skin papilloma develops in the course of a few months to a year into a malignant tumour. The virus which is readily obtainable from the wart and will cause the formation of new warts has not been extracted from the malignant one, being apparently neutralized. Rous has also shown that if the papilloma virus is injected intravenously in rabbits which have developed warts fol-

lowing painting with tar malignancy develops rapidly at the site of the wart. The simplest interpretation of this is that the skin cells are so altered by tar as to be in the state requisite for the immediate manifestation of malignancy.

Radiotherapy.—The discovery of the nature of the primary effect of radiation on the processes of cell life is of paramount importance, since more exact knowledge might lead to a more effective form of radiotherapy. It is known that enzyme systems differ in their vulnerability to radiation and the two main systems supplying energy to cells, namely, respiration and glycolysis, are differentially attacked and the utilization of carbohydrates is inhibited by radiation. Finally, an experiment is quoted to show that the effects of small doses of radiation are cumulative and the period of recovery from slight damage is longer than used to be thought.

ARNOLD BRANCH

Editorial Comments

Health Examinations for College Students in New Brunswick

The *Journal* has for some months past been giving attention to the subject of the health of college students, in particular, with regard to tuberculosis.* Our comments, so far as Canada is concerned, were based on information kindly submitted by the deans, professors of medicine and directors of physical education in some of our largest educational institutions, but we recognize that our survey was incomplete. Through the courtesy of Dr. William Warwick, Chief Medical Officer of New Brunswick, we are now enabled to give additional facts and figures relating to that Province. To New Brunswick, we believe, goes the credit of being the first to institute physical examinations of all entering students, with the view, primarily, of detecting cases of tuberculosis. This was in 1926. It is worthy of note, that unlike the situation in some other communities, this innovation originated in the zeal of the Public Health Department. The following quotation from an address given by Doctor Clark, District Medical Health Officer, New Brunswick, at the meeting of the Canadian Public Health Association held in Ottawa last June, is illuminating.

"In 1926, at St. Joseph's College 76 students were examined and x-rayed by travelling tuberculosis diagnosticians of the Department of Health, and 3 cases of active tuberculosis were found. In 1928 the Provincial Normal School and Mount Allison University were surveyed. Since that time practically every college and university has been added, so that students entering their first year are given a general physical examination by the field staff of the Department of Health, and their chests are x-rayed by means of a portable x-ray unit owned by the Department. The Normal School students are given lectures on tuberculosis by one of the District Medical Health Officers. A total of 6,571 students have received such examinations, of whom 66 were found to have active tuberculosis. To our knowledge, New Brunswick was the first province to institute chest x-ray examinations for all first year college students, although the number may not be the largest on record. The discovery of tuberculosis in the students is important, but it forms but a small part of the value of such surveys. The future school teachers and college graduates will exert a great influence on every community in the province. The routine examinations stimulate interest among this group, and it is hoped and expected that they will spread information about tuberculosis after their graduation."

* *Canad. M. Ass. J.*, Various editorials, 1936, 35: 313, 553; 1937, 36: 623; 1937, 37: 180.

The accompanying Table is of interest.

COLLEGE AND NORMAL SCHOOL SURVEY IN
NEW BRUNSWICK

Year		Examined	Active tuberculosis
1926	St. Joseph University....	76	3
1928	Provincial Normal School.	227	0
	Mount Allison University..	110	0
1929	Provincial Normal School.	334	1
	Mount Allison University..	138	0
1930	Provincial Normal School and Colleges	601	7
1931	"	825	9
1932	"	645	5
1933	"	608	7
1934	"	1,146	9
1935	"	1,071	15
1936	"	790	10

Such work in the different institutions of our land is all to the good and those active in it deserve commendation. But we wish that, when circumstances permit, the practice will be extended so that all our college students will be physically examined, not once, on entrance, but yearly throughout their course, and by both x-ray and tuberculin. It is all very well to examine students on entrance, but much may happen in the subsequent four or five years of their sojourn in college. Tuberculosis is a treacherous disease and may blossom forth at any time, and most unexpectedly; hence the necessity for more than the ordinary follow-up of suspicious cases. Extended examinations of the kind here recommended will cost money, but they will be worth it.

A.G.N.

The Canadian Medical Protective Association

The Canadian Medical Protective Association is one of the off-shoots of our Canadian Medical Association upon which we may well pride ourselves. Its value to the profession has for long been established, and seems to be increasing year by year.

According to its Constitution the C.M.P.A. has certain general objects before it: (a) to support, maintain and protect the honour, character and interests of its members; (b) to encourage honourable practice of the medical profession; (c) to give advice and assistance to and defend and assist in the defence of members of the Association in cases where proceedings are unjustly brought or threatened against them; (d) to promote and support all measures likely to improve the practice of medicine. In pursuance of these objects the Association undertakes to assist in defending civil actions for damages for alleged malpractice in the practice of medicine and surgery, where such actions appear to the Executive Committee and to the General Council of the Association to be unjust, harassing or frivolous, or where it appears otherwise to be reasonable to afford the

member whose conduct is impeached an opportunity of defending himself before a court of law. The Association, undertakes, subject to its by-laws, to pay the taxable costs of his defence reasonably and properly incurred exclusively on his behalf, together with reasonable and proper witness and counsel fees, and may assist in the payment of the whole or any part of damages, if awarded, and may assist in any appeal to a higher court from a verdict rendered. The great value of such service is sufficiently obvious.

The Thirty-sixth Annual Report of the C.M.P.A. is before us. A few points brought out therein merit the special attention of the profession. We quote. "Careful work and adequate records of all cases treated are the greatest safeguards against litigation." An important statement is that relating to sponges. "Because the counting of sponges should now be a routine procedure in all hospitals the Executive Committee has decided that they will not defend any member where he is sued because a sponge has been left in the abdominal cavity unless a sponge count is a routine procedure in the hospital in which he works. This does not mean that the Association is neglecting these members. It simply means that every surgeon must insist that a sponge count be a routine part of the operative procedure for his own hospital. All courts nowadays regard the omission of this precaution as negligence pure and simple, and no adequate defence can be offered when it occurs. With regard to smaller sponges and gauze used for drainage purposes which are overlooked and which cause trouble it seems only reasonable to remind members that these should be noted carefully when left in the wound, and instead of stating 'drainage removed', for example, the post-operative notes should state what and how much has been removed. This ordinary precaution should suffice to prevent overlooking small sponges in abscess cavities, etc." X-ray examination is a necessity in the case of injuries in which fractures are possible but not obvious, and after the reduction of fractures. Fluoroscopic examination is not sufficient. Attention is also called to the statute of limitations, operative in all the provinces with the exception of Quebec, whereby a patient is prohibited from bringing suit against a doctor for malpractice or negligence unless this suit is instituted within one year from the time the treatment complained of terminated.

Some remarks contained in the report of the General Counsel of the C.M.P.A. relative to professional secrecy in connection with contract work are worthy of special attention.

"First, the examination of prospective employees to determine their physical fitness for the employment proposed—where a medical man is acting on behalf of a corporation which

has its own medical officer the medical man should complete the details of the report as required by the medical officer of the corporation, but, for his own protection, he should keep a complete record of the examination for inclusion in his files. In this case he is acting for the medical officer whose opinion is to be decisive.

"Where the medical man is reporting direct to the prospective employer he is the sole authority and his opinion on all medical grounds is final. Therefore the material upon which his opinion is based is properly in his custody and should remain so without any disclosure. All that is relevant and necessary for the employer to have is a categorical certificate that in the opinion of the medical man the applicant is fit or unfit for the employment proposed. The medical man should retain in his own possession the detailed medical history sheet containing all the results of his examination, but he may, if he wishes, hand a duplicate copy to the man examined in order that he may consult his own doctor and, possibly, through that medium, produce further information to satisfy the original examiner that a favourable certificate should be given.

"Second, where contract work relates to the examination and other medical services in the case of those already employed—Absolute professional secrecy should be observed with reference to all information obtained by the medical man in the exercise of his professional duties, and the only departure from this rule would be when the employee has given his consent. When this occurs the medical man should put the information to be disclosed in writing and give it to the employee to deliver to the employer if he sees fit.

"Disclosure may be required by statute, or by a court of law, or on exceptional grounds of public policy, but the sound rule to follow is to disclose no information obtained in the course of professional duties unless the court shall so order or your Executive Committee on reference shall so advise."

Membership in the Canadian Medical Protective Association costs only \$5.00, a sum

ridiculously small in view of the amount of protection received. The low cost is due to the fact that the C.M.P.A. is an organization on a mutual basis, which in this case means non-profit making. The C.M.P.A. is not an insurance company. The members do not receive a policy but are entitled to whatever assistance they may require. The financial statement shows that the reserves are more than adequate for its needs, more particularly when it is realized that by means of reinsurance the Association is protected against a greater loss than ten thousand dollars in any one year.

In these days when the doctor's services are being increasingly scrutinized, and reasons, good, bad, or indifferent, are apt to be advanced to avoid the payment of medical fees it is the part of wisdom to be insured against legal proceedings. Even if an action against a doctor be dismissed it proves a costly experience for him at best. Better take the obvious precaution. You may be next!

A.G.N.

Medical and Hospital Care of Travelling Artists and Performers

It has been brought to the attention of the Executive Committee of the Canadian Medical Association that artists and performers in the employ of travelling companies or groups are very often injured in the performance of their work, and in most instances there is no provision made at the present time by which the medical man or the hospital can collect payment for services rendered to such persons. In several instances these uncollectable accounts have amounted to hundreds of dollars.

It was agreed by the Executive Committee that this warning statement should be published in the *Journal*, advising doctors attending artists and performers suffering injury while in performance of their work that they should take the necessary steps to protect themselves with regard to the payment of their accounts.

G. H. AGNEW

ACUTE ULCUS VULVÆ.—A. Crosti accepts as a clinical entity the occurrence of acute vulval ulceration due to the *B. crassus* of Lipschütz. It is most common in girls or young women, and is not conveyed by coitus. Acute painful ulcerations, which in the majority of cases are gangrenous, affect the vulva, and there is a variable degree of general prostration and pyrexia. The course is invariably benign, but relapses may occur. Diagnosis and etiology present difficulty. The bacillus of Lipschütz is usually present—often in nearly pure culture. It is cultivable in agar-ascitic fluid and sugary media and produces much lactic acid, but it is easily

confused with (and has been said to be the same as) Döderlein's bacillus. The Lipschütz bacillus, however, has been recovered from the blood and from the aphthous oral ulcers which sometimes accompany the vulval ulceration. Of this a subacute form resembling venereal streptobacillary ulceration, and one with small superficial ulcerations, have been described, but are less common than the gangrenous form. A general rash, usually papulo-erythematous or vesicular, but sometimes pustular, may be present. Cure is always speedily obtained by weak antiseptic applications and by rest.—*Athena*, May, 1937, p. 210. Abs. in *Brit. M. J.*

Special Article

ANTERIOR POLIOMYELITIS IN ONTARIO

By J. T. PHAIR, M.B., D.P.H.

*Chief Medical Officer of Health,
Ontario*

Until late July there was no evidence to confirm the prediction that acute anterior poliomyelitis would, in keeping with the cyclic character of its visitations, occur in epidemic proportions in Ontario this year. Thirteen cases were reported for the six months ending June 30th. During July 10 cases were reported during the first two weeks and 28 during the last two weeks. Beginning with the first week in August, there was an abrupt rise for each week up to the time of writing (September 11th) as follows: weeks ending August 7th, 57; August 14th, 73; August 21st, 230; August 28th, 336; September 4th, 388, and 47 cases reported late for the week ending September 4th, which gives a total of 1,169 cases for the period from July 1st to September 4th. Using the serum-distribution as an index, it is safe to presume that this number will be increased by an additional 250 cases when reporting for the week ending September 11th is completed; bringing the total number of cases to approximately 1,450. This incidence is more than ten times as great as for comparable periods in non-epidemic years. In comparison with 1929, when the disease was prevalent in Ontario, there have been seven times as many cases up to the end of August. In comparison with 1930, when the most extensive previous outbreak occurred, there have been three times as many cases for the corresponding period.

The geographical distribution for the month of August shows 54 per cent of cases in Toronto and suburban areas. The Niagara Peninsula and the area along the counties bordering Lake Erie as far as Elgin show an increased incidence.

In the district surrounding the City of London a marked increase in the number of cases has also been reported. Central Ontario remains fairly free. The eastern section of the province has, however, had an appreciable increase in the normal prevalence rate. With the exception of the City of Sudbury and the adjacent district but few cases have to date been reported from the northern and north-western sections of the province.

The disease is fairly typical in its early manifestations, with the preponderance of the cases showing premonitory symptoms consisting largely of fever, headache, drowsiness, muscle-soreness, accompanied by some gastro-intestinal upset, usually consisting of nausea, vomiting, constipation and distaste for food. Injection of the nasopharynx and sore throat may also be present. These symptoms are commonly followed at varying intervals by signs of meningeal involvement. Some 30 per cent of the diagnosed cases go on to paralysis of one or more muscle groups. How many cases showing only the early constitutional symptoms have been overlooked or untreated is impossible to estimate. In the large majority of the cases reported the diagnosis has been confirmed by spinal fluid examination.

The Provincial Department of Health has attempted to assist the health authorities and physicians in the affected areas by placing at their disposal the services of specially trained physicians to aid in the diagnosis of doubtful cases. These diagnosticians have been located at convenient centres in those sections in which the disease is most prevalent. Sixteen physicians are engaged in this service. The Department has, further, placed respirators at strategic centres, and is prepared to ensure rapid transportation to those centres of all cases showing evidence of involvement of respiratory muscles. Every effort is being made to ensure the maximum of early orthopaedic treatment in all cases with paralysis.

COFFEE AND LIQUOR.—H. Koopmann and H. Kemp-ski have carried out a number of investigations on the influence of the consumption of coffee on the concentration of alcohol in blood and urine in persons under the influence of drink. They were able to confirm the well-known sobering influence of coffee, which takes place in spite of the fact that the concentration of the alcohol in the blood remains unchanged. At the same time the alcoholic breath becomes less pronounced, though only

temporarily. The concentration of alcohol in the urine increases after the consumption of coffee and eventually becomes greater than the concentration of alcohol in the blood. Therefore, from the medico-legal point of view the concentration of alcohol in the urine is of no significance without a simultaneous examination of the concentration of alcohol in the blood in persons suspected of being under the influence of drink who have partaken of coffee afterwards.—*Munch. med. Wschr.*, May 14, 1937, p. 780. Abst. in *Brit. M. J.*

Men and Books

THE PIONEER DOCTOR OF ALBERTA: WILLIAM MORRISON MACKAY*

By HEBER C. JAMIESON, M.B.

Edmonton

"His excellent professional abilities will be greatly appreciated, in as much as they are combined with great professional zeal and much kindness and amiability of character." Such were the words used by Sir James Y. Simpson, discoverer of chloroform anaesthesia, and Professor of Midwifery at the University of Edinburgh, in recommending Dr. William Morrison MacKay, for a position in Scotland in 1861. Three years later Dr. MacKay, as a surgeon to the Company of Gentlemen Adventurers trading into Hudson Bay, arrived at York Factory, then staffed by a group of Scotsmen that could be counted on both hands. Later he penetrated the Great Northland and finally became the pioneer doctor of Alberta.

Few medical men had, previous to the coming of Dr. MacKay, remained long in the Western Wilderness. Several brought out by the Earl of Selkirk remained in the Red River Settlement. One spent a few months on Hudson Bay in 1812. This was Dr. Thomas McKeevor an "obstetrician adventurer" from Ireland. His experiences are on record.

Dr. William Todd, who joined the Company in 1816, was another Irish surgeon. Unlike his compatriot, Todd spent his life in its service. First on the Red River and later at Fort Wedderburn on Lake Athabasca he was Surgeon and Factor. Since Fort Wedderburn was just a mile from the present site of Fort Chipewyan he was the first medical man to reside in what is now Alberta. Details of his sojourn there are unavailable. In 1832 he returned to the Settlement. While here he confined the wife of Sir George Simpson. He was banished to New Caledonia later, since it was thought his eccentricities would do less harm there. Returning, he died in 1851.

Dr. John Rae, an Edinburgh man, joined the Company in 1834, and was first stationed at Moose Factory. Later he ranged from the Bay to the Red River and the Arctic. With Sir John Richardson he set out in 1848 on the search for Franklin. His work was to a large extent scientific rather than medical.

In 1869, when small-pox broke out in the

Edmonton District, there was no doctor nearer than Fort Garry, a thousand miles to the East.

Dr. MacKay was born at Stirling in the Scottish Lowlands in 1836, but he came of sturdy Highland stock. When ten years of age he was sent to Gillespie's preparatory school in Edinburgh. Before completing his elementary education he decided to make mechanical engineering his life work. But like many another whose plans "gang aft aglee", he accidentally lost the sight of one eye. Lying for weeks in the Infirmary attended by doctors and nurses he changed his mind and decided to study medicine. Entering Edinburgh University, he became a pupil of George Wilson, Regius Professor of Technology, and later was his junior assistant. Dr. John Brown, the author of "*Horæ Subsecivæ*", has given us a sympathetic picture of this Edinburgh teacher. He says of him that "truth of science was to him a body, full of loveliness, perfection, and strength, in which dwelt the unspeakable Eternal". "His great quality lay in making men love ascertained and recorded truth, scientific truth especially; he made his reader and hearer enjoy facts." Under such an influence did young MacKay begin his medical studies.

It is of more than passing interest to recall some of the other members of the Faculty. Perhaps never had the University a more brilliant group of medical men at one time. James Syme, the famous "excisor" of diseased joints, a man who "never wasted a word, nor a drop of ink, nor a drop of blood", was at the height of his fame. The journals of the time recorded his many remarkable operative procedures. One operation has been preserved in the writings of Dr. John Brown, who was then his assistant. In "*Rab and His Friends*" he tells of the notice which he himself posted on the wall of the first landing at Minto House. It read, "An Operation today,—J. B. Clerk". Then follows a classic description of a breast operation undertaken without an anaesthetic. Syme's career marked the end of a lustrous period in surgery. His assistant and son-in-law, Joseph Lister, opened another more splendid. Lister was a lecturer in Dr. MacKay's student days.

In other branches of medicine the Faculty at Edinburgh was outstanding. Three Monros in succession had occupied the chair of Anatomy for a period of 126 years. This subject had suffered from a progressive asthenia under *Monro tertius* "who unconcernedly at noon ate cranberry tarts in the midst of grinning students at a small pastry-cook's, and with digestion

* Presented at the first meeting of the Jamieson Medical History Club, Edmonton, Alberta, December 9, 1936.

unimpaired the next hour read his grandfather's essays on hydrophobia as part of an anatomical course". Better days were in sight, however, for John Goodsir presently occupied the chair of anatomy. Though little is heard of him today, his work in his own day was of such outstanding importance that Richard Virchow dedicated his work on cellular pathology to him "as one of the earliest and most acute observers of cell-life, both physiological and pathological, as a slight testimony of his deep respect and sincere admiration by the Author". The late Dr. Harry Goodsir McKid, of Calgary, the first Albertan to be president of the Canadian Medical Association, was a cousin. Then too, Sir James Y. Simpson, one of the great obstetricians of his day, the inventor of acupressure, and, as we have seen, the discoverer of chloroform as an anæsthetic, was in full career.

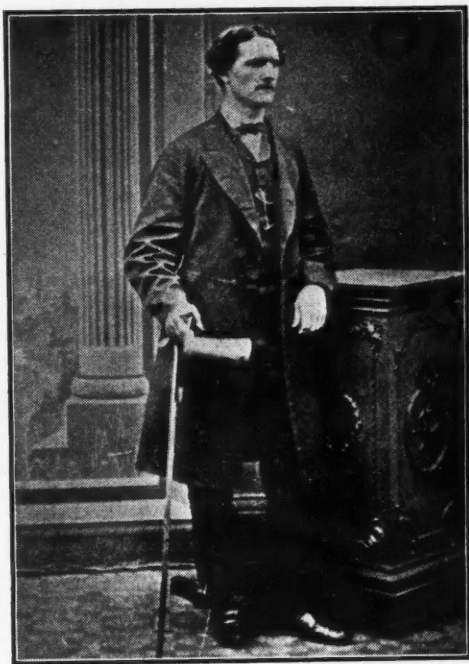


Fig. 1.—Dr. MacKay, 1864.

Under such tutelage young MacKay prosecuted his medical studies, and in 1858, at the age of 22, received his degree. For the next three years he was an assistant to Dr. William C. Fowler, a late lecturer on Medical Jurisprudence in the University, Aberdeen. Dr. Fowler was then in practice near Edinburgh. On seeking a post as surgeon to the Parish of Muthill, MacKay carried with him testimonials from many leading medical men in Edinburgh. From that of Sir James Y. Simpson, the opening quotation is extracted. He practised for a time at East Linton, evidently not having sufficient backing to get the post he sought. A chance meeting in Edinburgh with the General Secretary of the Hudson's Bay Company in London, who was a cousin, turned his

thought to the great company's operations in Rupert's Land. Like many another youth of those days his imagination had been fired by the tales of R. M. Ballantyne, who, after spending six years in the service of the Company, wrote "Hudson Bay" and "The Young Fur Traders". Such a life as there depicted sent many another young Scot across the Atlantic, to spend his happiest days hunting and trading in the far recesses of the mighty unknown wastes of British North America.

MacKay was told of the need of doctors in the North, and joined the Company as surgeon. On June 13, 1864, he sailed from London, having the night before attended the dinner which it was customary for the Company to give to the officers of their ships on the eve of their departure for Hudson Bay. The fleet consisted of three barques, the *Prince Albert*, *Prince Rupert* and the *Prince of Wales*. The



Fig. 2.—Dr. W. M. MacKay, the Pioneer Doctor, shortly before his death.

two former were sister ships of five hundred tons burden. Each was 103 feet long, 25 feet 6 inches broad, 17 feet 6 inches deep, and 6 feet 6 inches between decks, with a cabin 10 by 12 feet.

The voyage was long and eventful. The *Prince Albert*, carrying Dr. MacKay, ran on the reefs of Mansel Island at the entrance of the Bay, but was saved and reconditioned. It was on the *Prince of Wales* that John Richardson, later Sir John, who accompanied Sir John Franklin on his historic "Journey to the Polar Sea", was a passenger in 1819.

It is not known how many days it took the *Prince Albert* to reach York Factory, but on a voyage in 1845 it is recorded that thirty-seven days were spent in beating down the bay a

distance of six hundred miles. The barque which carried Doctor MacKay ran on a shoal, was floated at high tide, and when it arrived in port a large boulder which had lodged in its hull dropped out and the vessel had to be beached.

What little one can gather about York Factory during the doctor's stay is from the pen of Isaac Cowie, an old timer in the Company's service. Dr. MacKay arrived in 1867. He kept a diary during the greater part of his life in the North, but unfortunately it was lost after his retirement in Edmonton. His widow, who still resides there, remembers many incidents which he related. Cowie remarks that

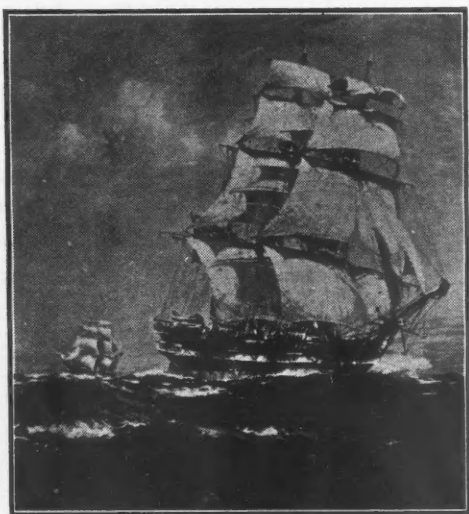


Fig. 3.—The Barque *Prince Albert*.

Dr. MacKay inspected the crew and passengers on the former's arrival at York Factory in 1867. This was a very necessary procedure, since it was a common occurrence for scarlet fever, measles, and enteric fever to break out at this port of entry and to spread to the families of the officers, and then to the half-breeds and Indians in the vicinity. Such outbreaks also happened frequently when the fur brigade arrived at any of the posts scattered throughout the great northern territory.

The officers fared well at York Factory. Fish, duck, geese and venison in generous quantity were spread before them. Milk came from their own dairy, and in summer rhubarb, lettuce, and radish grown in their garden added relish to the more substantial fare. At lunch beer or stout was served, while at dinner port and sherry went the rounds.

Shortly after Cowie's arrival Dr. MacKay volunteered for service in the MacKenzie River district, news having arrived of some mysterious disease among the Indians which was interfering with the trapping and consequently the buying of furs. The doctor was to winter at Norway House, one of the most important

posts in the West. Here the brigades from Fort Garry, the prairie forts, and those from the Athabasca and far off MacKenzie river centres met to deliver their furs, their mail, and gossip, and to receive in return the various goods used for barter with the Indians, dispatched from York Factory. Cowie gives a minute description of the preparations and a graphic picture of the trip. The voyageurs as usual were decked out in their picturesque costumes. Even the clerks, when travelling, wore grayish blue cloth capotes with silver plated buttons and a broad scarlet sash. Beautiful silk-worked, tanned moccasins completed their outfit.

The first night out there was a downpour of rain. The camp-fire was a miserable little one of driftwood, and Cowie was glad to accept the doctor's invitation to have supper in his tent. "As a campaigner of three years' experience, the doctor had everything comfortably arranged in his tent", writes Cowie. He produced a ham and some cured buffalo tongue before leaving York Factory. "After disposing of these and fortifying ourselves with wine, Land (a clerk) brought forth a concertina, upon which he was no mean performer, and we all joined in a singsong until about ten o'clock." Early next morning the cold wet tent was rattled down on their heads, and they were forced to dress in the open air. Scrambling aboard, they found in the sternsheets of the York boat, a kettle of hot tea, and some biscuits, which constituted their early breakfast.

On this trip Dr. MacKay got an insight into the mind and characteristics of the French half-breed and of his skill and prowess. One day they made a portage past Trout Falls, a sixteen foot drop, and, while at dinner, there was a rattle of oars. Soon the Portage la Loche brigade of four boats flashed by and took the cascade at full speed with a final flourish of the steering oar just before disappearing.

MacKay and Cowie tried their hands at towing, poling, pushing, and warping the boats upstream, but on the portages they were given the oars to carry as they had not yet mastered the portage strap. For three weeks they toiled upstream, then over the height of land, then downstream, before reaching Norway House. The French voyageurs worked from dawn until sunset on a diet that an unemployed man on relief today would not consider fit for his dog. Pemican, made of dried and partly pulverized buffalo meat mixed with tallow, was the food that appeased their gigantic appetites and supplied the energy for their strenuous work.

A busy winter at Norway House prepared MacKay for his long trip into the MacKenzie

district. He reached Fort Simpson in the summer of 1868. This Fort was one of the most important in the North, situated on the MacKenzie at the mouth of the Liard, a river with a drainage area almost twice that of the Ottawa, and itself almost as long. The doctor remained here for four years, living part of this time with Bishop Bompas. At Simpson there was one of the best libraries in the whole country. It contained about a thousand volumes.

The first year he was at Fort Simpson Dr. MacKay made a trip to Fort Liard, some hundreds of miles up the river, where he found much sickness and distress among the Liard and Nahanni Indians, the latter a fierce, untamed tribe, always distrustful of the fur traders. They have within the last few years been opposing the entrance of the prospectors

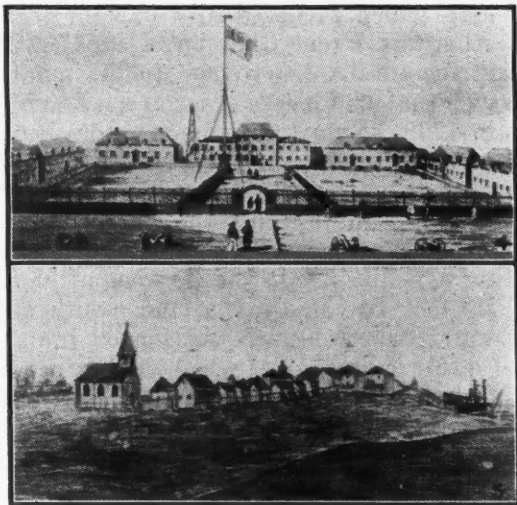


Fig. 4—York Factory, 1854.
Fig. 5.—Fort Chipewyan, 1890.

into the upper reaches of the rivers that course through their territory. These proud natives came in all their finery once a year, about June, in a picturesque line of canoes laden with furs to trade at Fort Simpson. During the long cold winter MacKay made excursions by dog-train to Fort Chipewyan and other posts in the district.

Dr. MacKay was married in 1874 to Jane Flett, daughter of William Flett, of Kirkwall, Scotland, who was later the Factor at York Factory. In the next year he was in charge of Fort Rae for nine or ten months. From there he went to Fort Resolution, where he remained for four or five years. A furlough of eleven months was spent at York Factory. About this time he made a winter journey with dogs to Isle La Crosse, over half way to Fort Garry.

In 1869 and 1870 small-pox, that scourge of all Indians, swept once again the Missouri and Saskatchewan regions of the West. Captain Butler, sent by the Lieutenant-Governor of the

Northwest Territories to investigate the situation on the prairies, reported a desperate state among whites and natives. When word of this outbreak reached Fort Simpson Dr. MacKay went south by dogtrain, arriving at Fort Carleton, which was near the Saskatchewan border of Alberta, east of Edmonton. Here he found one clerk dead and the pestilence almost over. He returned to Fort Simpson in March, and hearing of great sickness amongst the Indians at Great Bear Lake hurried north. He was back in the next spring, to go with the brigade to La Loche. The following autumn saw him at Fort Rae on Great Slave Lake. Here he wintered.

He spent a year at Dunvegan on the Peace River, and then went to Fort Resolution as Chief Trader in 1879. These frequent changes of location were made in order to give the Indians at each post the benefits of a doctor. It was only the most urgent cases of illness for which his services were asked by the Indians. Their medicine men, notwithstanding the best efforts of the clergy, both Catholic and Protestant, still carried on out of sight of the missionaries, even as they do today on the various reservations throughout the province.

Mrs. MacKay tells of one occasion, when one of the Company's employees was gored by a bull and suffered from a large gash in the abdominal muscles. The doctor selected his instruments—this was before his former teacher Lister had succeeded in convincing his colleagues of the value of antiseptics—and prepared to sew up the wound. When all was ready, he turned to his wife and said: "You're better at this work than I am, you sew this up". Accustomed as she was to the making of moccasins and the deerskin costumes of the country, Mrs. MacKay put twelve stitches in the belly wound, and was quite proud of the fact that the patient made a speedy and permanent recovery.

Frequently, when the Fur Brigade or the mail arrived at a Post epidemics broke out. Scarlet fever, measles, and dysentery ravaged the Post, and Doctor MacKay was called from his business duties to minister to the sick, not only of his staff but of the surrounding Indians. It was a trying time for him, but a fortunate circumstance for the Company that his medical knowledge was available at the far distant posts in these emergencies. On one occasion this was most distressing. His wife and six children were stricken with scarlet fever during a severe epidemic at Fort Chipewyan, and one child was lost. Mrs. MacKay remembers the paucity of drugs and their limited variety. Epsom salts, rhubarb, and grey powder served for many a patient whose complaints called for a more efficacious but absent remedy.

One catches glimpses of Dr. MacKay in the writings of several missionaries and travellers. The Rev. A. C. Garrioch, who was born in 1848 in the Peace River, and later returned as a school teacher to Fort Simpson and later still became an Anglican clergyman, when *en route* from Fort Garry to his first teaching assignment travelled from Lac La Loche down the MacKenzie River in 1874 with MacKay, who was in charge. He accepted the latter's invitation to share with him his mess, tent, and stern-sheets in the York boat. Garrioch had his violin, and it turned out that Dr. MacKay and Mr. Kenneth McDonald, one of the Company's officers, who had been an old college chum of the teacher's, could each play it as well. He writes:—

"One day, while we were afloat, I manœuvred for the Doctor's boat by saying to him after he had done his best with 'The days of Auld Lang Syne', 'Doctor, that was just fine. I do like that old tune when one puts some soul into it, as you do'. Then Mr. McDonald took his turn and played 'The Devil among the Tailors'. When he was through and had laid the violin across his knee, and the doctor, smiling and rubbing his hands had said, 'how very realistic', I said, reaching out my hand for the violin, 'please pass me over that fiddle and see how I'll electrify the fishes'. When I was through the doctor said, 'Well, I don't know what effect that may have had on the MacKenzie River fishes, but it was fine, and took my thoughts back to Aberdeen'".

In 1881, Dr. MacKay went to Scotland on a visit and spent the winter there. After his seventeen years from contact with medical thought and progress he was amazed at the changes wrought in obstetrics and surgery. Simpson had been dead eleven years, but chloroform was established in obstetrics and surgery. Lister, who had succeeded Syme in the chair of Edinburgh, and in 1877 went to London, had just applied his antiseptic principle to the surgery of the bones and joints, which did so much to extend the domain of surgery. Spencer Wells and Lawson Tait were outstanding surgeons at this time, while Pasteur had become world-famous, and Koch's reputation was fast increasing. What a change in medical science since he had buried himself in the woods of Canada!

On his return in 1882 he was placed in charge of Fort Dunvegan on the Peace River. After five years of service there he was moved to Grouard on Lesser Slave Lake. From Grouard, Dr. MacKay once took a winter trip to Edmonton, two hundred miles of it on skates. These skates were of local manufacture. Pieces of hard wood were shaped to fit the foot and with a saw a groove was cut in the bottoms and files set in and made secure. These skates were now bound with straps to the shoes. On these primitive gliders the employees of the Company often enjoyed exercise on the northern water courses.

Five years later he took charge at Fort

Chipewyan. Fort Chipewyan was for years one of the most important in the north, and its geographical situation is of special interest to Albertans for there the first settlement in the province took place. Peter Pond, then an independent trader, pushed his way far beyond the posts on the prairies in 1778, and arrived on the Clearwater, the only river in Alberta which runs west. He entered the Athabasca and followed it down to a large lake, referred to by the Indians as "The meeting place of many waters". This was Lake Athabasca, and on its bosom the currents of many rivers unite. From it flows the Slave to become the great MacKenzie River, the largest in Canada. Into the Slave pours the mighty Peace, with a course almost twice as long as that of the Ottawa. Lake Athabasca itself stretches half way across the Province of Saskatchewan, and has an area of nearly 3,000 square miles. In 1785 Peter Pond drew the first map which included any part of what is now Alberta. From Chipewyan in 1789 MacKenzie set out on his voyage to the mouth of the river that now bears his name. From here also, in 1793, he started his momentous journey to the Pacific by way of the Peace River. This historic fort was the outfitting depot for many explorers and hunters into the Barren Lands.

In 1889 Warburton Pike made his famous hunting expedition into the Barrens after musk ox. He met Dr. MacKay at the mouth of the Clearwater, where he was waiting on the stern-wheel steamer *Grahame*, which had superseded the York boats on the northern waterways as far as Fort Smith. MacKay accompanied Pike this far, and, embarking in a light canoe, they went down the old boat route, making some fifteen portages in a long afternoon. Later in the season, at Fort Resolution, Pike met Dr. MacKay, who was on his yearly round of visits to the outlying posts of his district. The following spring he received from the doctor a burning glass, a compass, a watch and half a dozen pairs of glasses to protect the party against snow-blindness. There were also axes, knives, and beads in case Esquimaux were encountered. On this journey Pike arrived at a large lake, unnamed on his maps. This he called Lake MacKay after the doctor who had done so much to ensure the success of his trip. This lake is about 1,000 square miles in extent.

In 1895 Caspar Whitney made a trip to the Barren Ground on snowshoes, and met Dr. MacKay at Chipewyan. The latter tried to dissuade the Whitney party from attempting to venture into the Barrens in winter. Finding advice of no avail, he made a contribution of greater importance—two of the post's best dog teams. With these Whitney made a successful trip. Just after the turn of the century J. W. Tyrrell arrived at Fort Chipewyan, to explore the sub-arctics of Canada. Dr. MacKay was away, but was expected any time on the

Grahame. A strong wind was blowing and a heavy sea running when the boat tied up at the pier after dark. The doctor disembarked and declared that it was the last time he would ever be a passenger on her in such weather. This, perhaps, was not an unwise resolution, since the steamer was top-heavy and drew only about three feet of water, and was not unlikely to roll over in rough weather. MacKay supplied Tyrrell with the best guide available.

For ten years Dr. MacKay remained in charge of this important post, retiring to Edmonton in 1898. So valuable had been his service to the Hudson's Bay Company during his thirty-four years as Surgeon and Factor that a post between Fort McMurray and Fort Chipewyan was named after him. Ill-health restricted his activities for some time, but later he was able to enter practice. On January 15, 1902, at a meeting in Edmonton, the few practitioners in that city and vicinity organized the North Alberta Medical Association, with Dr. W. M. MacKay as its first president. This was the parent society of the present Edmonton Academy of Medicine. On February 25, 1917, following a fall on an icy sidewalk Dr. MacKay passed away. He is survived by his widow, two sons, and six daughters.

Fifty-three years of self-sacrificing practice, nearly all spent in the north country, should assure this hardy campaigner a place at the top of the list of pioneers when the medical history of the West is written.

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University Notes

Manitoba University

Dr. Donald J. Bowie, of McGill University, has been appointed assistant to Dr. I. MacLaren Thompson, head of the department of anatomy in the medical faculty.

A graduate of the medical college of the University of Toronto, Dr. Bowie also holds the degrees of Master of Arts and Doctor of Philosophy in medicine from that institution. He studied, as well, at the University of Bern, Switzerland, and has published the results of personal researches into the pancreas, blood vessels and glands of the stomach.

ROSS MITCHELL

Association Notes

The Belfast Meeting of the British Medical Association

This year's meeting of the British Medical Association was held in Belfast during the last week in July, and the general impression left upon the mind of the writer is that it was eminently successful. New Zealand is said to be more English than England itself, and the spirit of loyalty in North Ireland is perhaps greater than in any other part of Great Britain. So it was at any rate in the days of Carson, and so it seems to be still. One imagines that it is sharpened on the grindstone of neighbouring opposition to the south. In any case it was observed that the men and women of Belfast, both medical and lay, had united in preparing the utmost of hospitable welcomes to the Association collectively and to its members individually.

Belfast itself, although chiefly an industrial city, is situated in charming scenic surroundings, with a river and the sea at hand, and lovely hills in the distance. In the city there were tours of inspection through the establishments of the great industries for which Belfast is famous: the Harland and Wolff ship-building yards (largest in the world); the linen factories; and Gallaghers' tobacco factory, among others. Numerous excursions were arranged to the Giants' Causeway, various castles, and other points of scenic and historic interest. Hotel accommodation was somewhat limited, but private hospitality came nobly to the rescue. The Housing Committee had worked for ten months upon this problem, with the result that everybody was happily accommodated.

Once more one realizes what a very large power for good is the B.M.A.; its branches seemed to be conterminous with the Empire. Representatives were present from all parts of Australia; from New Zealand; South, Middle, and North Africa, including Tanganyika Territory, which used to be German; from all parts of India and the Malay States; from the Mediterranean islands, Malta, Cyprus; from Ceylon; from the British West Indies, and, finally, a few, very few, from Canada. In Canada, however, our own Association forms so large a body and is of so national a calibre that it would seem a work of supererogation to maintain on the side, as it were, special branches of the British Association. Several such branches existed and did useful work in our earlier, somewhat unformed, history, but with the large and rapid growth during the past generation of the Canadian Association, died gradually a death which was not unnatural under the circumstances. Yet our relationships with the B.M.A. have been always so cordial that no subsidiary

or affiliated relationship could increase either cordial feeling or active cooperation.

As to the scientific part of the program the usual high level was maintained. The writer can speak only about the work of the surgical section. In contrast with the American societies, which accept a large number of papers, and work from nine to five every day of the meeting, the British Association has always adopted the principle of working half the day and devoting the other half to the amenities of life. It is the English point of view, and who shall say that it is less worthy! The tendency of the Program Committee in the B.M.A. is to decide upon one broad subject for discussion on each day, to appoint two or three leaders or openers of the discussion, then to leave time for general members to take part in that discussion. All this occupies a considerable part of the three-hour session, and, consequently, time is left for only a few of what is called "occasional" papers on special subjects as offered by individual contributors. Upon these last there is very rarely any general discussion.

In the Belfast meeting the first day was occupied largely by a symposium on the surgical treatment of peptic ulcer, which was introduced by Professor Morley, of Manchester, followed by Mr. Lake, and Mr. Ogilvie, of London, and Dr. Carl Semb, of Oslo, Norway. Nothing outstandingly new was brought forward, which, indeed, was hardly to be expected in the present flux of opinion; but the various opinions expressed, and supported by careful statistics of a large experience, contributed definitely to the formation of those conclusions towards which all surgeons are looking, namely, what is the most promising thing to do under different sets of circumstances. The level of the discussion, including as it did numerous data upon the physiological and pathological sides of the problem, was worthy of the occasion. Dr. Semb's observation that partial gastrectomy gave better results than gastrojejunostomy, with a mortality rate as low, was particularly interesting; but he found that the former was followed by some degree of anæmia in 45 per cent of the cases, and there was a difference in this respect between male and female patients. Whereas 25 per cent of male patients had an anæmia usually of slight degree, 70 per cent of female patients presented anæmia which in 35 per cent was severe.

An "occasional" paper on gastroscopy in dyspepsia, presented by Mr. H. W. Rodgers, was decidedly in favour of the method, which he maintained was particularly necessary where radiology had failed to reveal a lesion. Mr.

Edwards was even more emphatic in support of the method.

On the second day the chief subject for discussion was obstruction of the common bile duct, opened by Mr. E. R. Flint, of Leeds, followed by Mr. Howard Stevenson, of Belfast, and Mr. Gordon Taylor, of London. Four occasional papers were also presented: upon duodenal regurgitation, the treatment of severe burns, the Steinach operation for prostatic symptoms, and section of the sphincter of Oddi for relief of pain following cholecystectomy and for recurring pancreatitis.

Professor Henry, of London, said that in regard to the toxæmias of burns it had been found that the blood in some of these cases contained four times the normal amount of histamine, and that this increase did not occur till the fourth day after the accident, the most dangerous period where initial treatment has been successful. He associated the histamine increase with the increase of acid in the gastric juice. Massive doses of soluble alkali had given strikingly good results.

On the third and last day the symposium, which combined the sections of medicine and surgery, was upon abscess of the lung, opened by Dr. Burrell and Mr. Roberts, of London, followed by Dr. Kerley, of London, Dr. Semb, of Oslo, Dr. Geoffrey Marshall, Dr. Burton Wood, of London, Mr. Purce, of Belfast, and Dr. Archibald, of Montreal. Mr. Roberts represented the rational, though radical, view of modern surgery in his opinion, that, while thoracotomy with external drainage was the method of choice in the earlier stages, lobectomy was the best procedure in many of the more chronic lung abscesses. He was in favour of early thoracotomy and drainage, placing a limit of observation at two weeks, whereas Dr. Burrell demanded six weeks. Semb agreed with Roberts. Again it may be said that although no great advance was announced as the result of this general discussion the various speakers did contribute very definitely towards clarifying and establishing standard modes of treatment for the different types of abscess of the lung. It was obvious, however, that in general the notorious failure of many lung abscesses to heal spontaneously or under medical treatment was forcing the medical man to consider seriously more radical surgery, that is, practically, lobectomy, as the proper and only recourse; while on the other hand the recent success of the surgeon, not only as regards definite cure but also as regards the immediate mortality of the operation, was certainly giving more encouragement towards so radical a decision.

E. W. ARCHIBALD

Provincial Association Notes

The Saskatchewan Medical Association

The Saskatchewan Medical Association and the College of Physicians and Surgeons of Saskatchewan met in Regina for their thirtieth annual meeting. About 170 members were present. Dr. D. M. Baltzan, of Saskatoon, President of the Saskatchewan Medical Association, presided at the business meeting. He outlined the steps taken last year when the Association, by a vote of 125 to seven, decided to amalgamate the Saskatchewan Medical Association and the College of Physicians and Surgeons of Saskatchewan. Among those who spoke opposing the amalgamation were Dr. D. S. Johnstone, and Dr. S. E. Moore, both of Regina, and Dr. G. R. Peterson, of Saskatoon. A proposal to circularize all the profession and have a ballot by mail on this subject was discussed. It was pointed out that the annual meeting is the place to do business, and any member who is not interested enough to attend the meetings should not complain if motions are passed which do not meet with his approval. A standing vote was taken and the amalgamation of the Saskatchewan Medical Association with the College of Physicians and Surgeons of Saskatchewan was consummated.

The report of the committee which had been appointed to look after the question of payment to doctors for work among the indigents was received. The committee has divided the doctors into three groups: A. those working in the country drouth area; B. those working in towns who, in addition to their town practice, drive out to the country and who also do surgery upon indigent patients in the town hospital; C. city doctors who are treating referred cases from the country for diseases in which they are particularly interested. This committee has waited upon the Provincial Cabinet and have been promised early consideration.

Mr. Arthur Moxon, K.C., of Saskatoon, addressed the luncheon meeting. He pointed out that the lawyers did no free work because they had to live, but that if the doctors gave up free work they could no longer boast about being noble and unselfish. While tuberculosis, cancer and venereal diseases had been given over to the Government to care for, he doubted if there was very much financial reward in this work anyway. Purely physical problems, such as poisoning grasshoppers or feeding the poor, can be easily accomplished by governments, but when it comes to social and economic complexities that deal with the heart and the mind and soul of people, the government cannot deal so simply with them. The parish had been chosen as a unit of relief in the days of Queen Elizabeth. Up till now it has been looked upon as

the suitable unit long after we know that it is not the proper unit. Mr. Moxon's address was like a breath of cool, fresh air, blowing through the confused sentimentalities of the medical profession.

The old-timers, that is, doctors registered in the North-West Territories before 1905, were the guests of honour at "The Old-timers Supper". The following were made life members: Drs. David Low, Regina; T. A. Patrick, Yorkton; H. A. Lestock-Reid, Prince Albert; A. W. Allingham, Broadview; G. H. Craig, Broadview; A. E. Cantelon, Piapot and Stoughton; and A. W. Argue, Grenfell.

Dr. J. A. Valens, of Saskatoon, gave a history of the early practitioner from the beginning of settlement until the time that Saskatchewan became a province. Dr. T. A. Patrick, of Yorkton, outlined his experiences as a young practitioner among the early Hebridean settlers at Saltecoats about fifty years ago.

The Hon. T. C. Davis told of his trip to the coronation at a luncheon. He felt that the solidarity of all the British dominions had been a great object lesson to all the other European powers, and that Anglo-American friendship was a necessity for the continuation of democracy. Dr. T. H. Leggett, of Ottawa, President of the Canadian Medical Association, addressed the final banquet. He stated that we were approaching a shortage of professional people in Canada and that the doctors must take the lead in solving economic problems of medical service. Room 101 was a popular rendezvous and many professional jealousies were dulled or drowned in C_2H_5OH .

A symposium on Arteriosclerosis was arranged by Dr. J. C. Paterson, pathologist to the Regina General Hospital. Dr. Paterson spoke on the "General pathology"; Dr. H. C. George, on "Coronary and aortic sclerosis" (including coronary thrombosis); Dr. S. Larson on "Cerebral atherosclerosis"; and Dr. L. A. Chase spoke on "Peripheral (diabetic) atherosclerosis".

Dr. C. H. Andrews, of Prince Albert, gave a paper on "The treatment of non-tuberculous pulmonary conditions". Dr. Andrews had spent some time at Dr. Chevalier Jackson's bronchoscopic clinic in Philadelphia. He now does the bronchoscopic work at the three Saskatchewan Sanatoria. Bronchoscopy, said Dr. Andrews, is a minor procedure. The indications for its use are unexplained chest symptoms, unexplained physical signs, and unexplained x-ray signs. By using the bronchoscope the source of fungi and of spirochaetes may be found; material for vaccines which is purer than that coughed up is obtained. If malignancy of the bronchus is suspected a sample may be taken for biopsy, but a normal bronchus should not be cut to obtain biopsy material. The bronchoscope may be used for selective bronchography, and it also

may be used if a foreign body of non-opaque character is suspected in the lung. There are no contraindications except aneurysms and cardiac hypertension, but if a foreign body is present even in these cases it should be used. Bronchoscopic drainage in lung abscesses or in bronchiectasis may be done once a week for six weeks. In bronchi the plugs of mucus become infected, then they melt, then they are coughed up. These plugs may be moved by the bronchoscope before the infected stage is reached. The cough of asthma may be investigated. Dr. Jackson says, "All is not asthma that wheezes". Adrenalin and cocaine may be applied to swollen bronchi. It flattens them out and improves them for some weeks. The bronchoscopic complications of tuberculosis are similar to those of the larynx. The tissue is swollen and thickens. Tuberculous and scar tissue may be present. These facts explain poor results in collapse therapy. When a foreign body goes into the lung, if it is metal there may be a symptomless period as long as four months, but if it is vegetable there will be symptoms in four hours.

Dr. M. R. MacCharles, of Winnipeg, gave a paper on "Diverticula of the colon". He said in his experience 10 per cent of all people over 35 years of age who had a barium series showed diverticulitis. It is common in fat men. The diverticula become inflamed. They are long barrel-shaped protrusions. After inflammation they may rupture from an abscess. This abscess may burrow out into the bladder, into the vagina, or into a loop of ileum. In diverticulitis there is pain in the left lower quadrant, no vomiting, no local tenderness. Later there may be distension and obstruction. A barium meal is better for diagnostic purposes than an enema. A sigmoidoscope helps to rule out carcinoma. There is not often a loss of weight. The early treatment is medical—the administration of petrolatum, low-residue diet and barium. In the acute conditions, such as obstruction, colostomy should be done. If there is an abscess, do a drainage with colostomy, and later on a resection. If there is a fistula do a colostomy, and after the fistula has closed, which takes six months or a year, a resection may be done.

Dr. W. H. Wardell, of Moose Jaw, gave a paper on "Intra-pelvic protrusion of the acetabulum".

Dr. W. D. P. Griggs, of Lipton, gave a paper on "The incidence of goitre in a rural community". Lipton is fifty miles north-east of Regina on the north slope of the Qu'Appelle valley. Its elevation is 2,000 feet. The iodine has been washed away from the land by many centuries of rain. The plains of Saskatchewan are old in glacial time. The district has a population of 1,950 and of these 260, or 13.3 per cent, are known to have goitre; the incidence is probably higher. Of these 220 have endemic goitre; 175 are female, 85 male. Of 371 school

children 103, or 28 per cent, have goitre. The population may be divided into four groups. The German or central European group, comprises 67 per cent of the population; 30 per cent of these have goitre. The British population comprises 28 per cent; 12 per cent have goitre. The Jews comprise 4 per cent, and 30 per cent have goitre.

Goitre is far more prevalent on the farms than in the villages. Thirty to 44 per cent of the inhabitants of the farms have goitre, and 6.8 per cent of the inhabitants of the village have goitre.

The Department of Mines of the Federal Government, in a survey of the wells of the district, found that no iodine was present in the water. The water is also highly contaminated with bacteria and has a high mineral content. McCarrison has shown that pollution of water plays an important part in thyroid enlargement and renders iodine inaccessible. Many of the wells are poorly constructed and too close to the barns. The farmers haul water two or three miles in barrels and tanks. These same tanks are used for hauling slough water. About thirty families use one well dug in the bed of a slough twelve feet deep. Water surrounds this well and spring. It is bailed out with buckets, and the farmers use the same buckets to water the stock. The ground about is trampled with horse manure. The water is therefore highly contaminated and unfit for human consumption. Some may say that the people should not be allowed to use this, but there is no other source of water. However, during the last two months this well has been reconstructed in a proper manner.

In one family, consisting of mother, father, and eight children from two to seventeen years of age, the mother has a goitre, and several of the children have goitre; five have large tonsils. During the last five months this family has boiled the water and has been given iodine; two of the children now have no detectable thyroid enlargement.

The country people use their own food and vegetables grown on their own land. The villagers have more imported fruit and vegetables. The German families use several hundred pounds of cabbage a year. It has been shown that cabbage contains organic cyanides which retard tissue oxidation; therefore more thyroxin is needed. The rural people do not get as well balanced a diet as those in the village. Most of the children carry a noon lunch to school, consisting of sandwiches and a piece of cake, with, possibly, the addition of a hard-boiled egg. Thus it is seen the school child's diet is deficient in vitamin C.

While the water of the village wells is high in bacterial count it is carried to the homes fresh in pails and does not sit around in tanks and barrels. Many of the people have been persuaded to boil the drinking water. The

School Board is buying potassium iodide tablets and the school children are given these according to the needs of the case.

Dr. G. G. T. Binning, of Saskatoon, gave a paper on "The examination of the school child". There are 5,808 school children in Saskatoon. He believes that by the physical examination of a school child he can almost guess what city the child comes from, because he knows the type of medical health work done in all the other Western cities. Those with the poorest physical condition come from rural Saskatchewan. There are three ages at which the child is examined. A pre-school entrance examination is done; 80 per cent of the children are examined before admission to school; they are examined again in grade 4 and grade 7, and, in addition, any child whose school nurse or teacher or parent thinks he needs an examination gets one. Twenty minutes is spent with each child. The child is stripped to the waist and the shoes are taken off. Wooden calipers are used for width measurement. Routine tuberculin testing is done. In 300 children 3.6 per cent showed a positive tuberculin test. If the test is positive a chest plate is taken to rule out active tuberculosis. A school clinic is not a diagnostic clinic.

A study was made in one school with 660 pupils, which was chosen because it was an average school as to race and social conditions. Eighty-nine per cent of the absences from school were due to illness; communicable diseases and infections accounted for 12.8 per cent of the time lost; colds and respiratory infections accounted for 33.6 per cent. The pupils were divided into classes, A, B, C, D, according to the economic standing of the parents. Class A included the well-to-do, which were 1.5 per cent of all pupils; they had 0.3 per cent of the illnesses. Class B was the moderately well-to-do, which were 24.3 per cent of all pupils; they had 10.5 per cent of the illnesses. Class C were those whose parents earned \$50.00 a month or less (they were entitled to free dental care) and included 63 per cent of all the pupils; they had 76.9 per cent of the illnesses. Class D were those on relief; they had 12.1 per cent of the illnesses. About 10 per cent of all pupils are below average intelligence.

Since Dr. Binning has been doing this work in Saskatoon six school children have developed malignancy; four of these were diagnosed in school. Of all defects discovered 69 per cent are improved or cured. The cost of the medical services is 2 per cent of the average cost of education in the city. This includes one full-time doctor, one full-time dentist, one full-time dental nurse, and three school nurses. It is only a few hundred dollars more than the cost of lights, water, laundry and telephones. Last summer 37 known cases of trachoma in school children moved into Saskatoon. These were all

visited by the school doctor who found twelve cases of trachoma in children in addition to those reported to him by the M.O.H.

Dr. J. D. Adamson, of Winnipeg, gave a paper on "The classification and treatment of anæmia". Hypochromic anæmia is due to iron deficiency, or bleeding, or deficient iron-intake, or chronic infection. Some patients seem to have an inherent condition of iron deficiency. The red-haired blondes are the commonest type to have this condition. The patients have blue sclerotics, atrophic tongues, dry lips, brittle striated nails. They like dry food such as oatmeal. The spleen is palpable in 15 per cent of them, and some have achlorhydria. The treatment is iron in sufficient doses. As reduced iron pills are one-third iron, 20 five-grain pills would be sufficient, or ninety grains of iron or ammonia citrate would be enough. This disease is found in girls who work in stores, in nurses, and in laboratory technicians.

LILLIAN A. CHASE

Medical Societies

The Saint John Medical Society

On August 18th, Dr. C. H. Best, of the Banting Institute, appeared at the meeting of the Saint John Medical Society, held in the Admiral Beatty Hotel, and in a most delightful informal manner presented the results of some research work done by himself and his colleagues, under the title, "Experimental work on thrombosis". Dr. Best related how this problem was attacked, using direct crushing injury to a vein, and chemical irritation to vein structures, and then showed how thrombus formation had been achieved in extra-corporeal loops or shunts made of glass, cellophane, and collodion.

He discussed the discovery and preparation and purification and crystallization of a substance called "Heparin", which substance controls or defeats the formation of thrombi, when introduced in the circulation as part of intravenous saline medication. He stated that such treatment was being tried in human beings in cases of splenectomy, partial gastrectomy, and in obstetrical practice in selected cases.

Dr. Best illustrated his subject with lantern slides and a motion picture film which demonstrated the collection and agglutination of blood platelets in the formation of the white thrombus.

For this summer meeting, there was an attendance of 40 members, who were much interested in this demonstration and physiological research, the hoped-for results of which, promise to be of much practical services in surgical practice. The Society felt that it was

fortunate to be honoured by Dr. Best, who had broken his holiday to be present with the Society.

On August 26th, the second summer meeting of the Saint John Medical Society was held in the Admiral Beatty Hotel. Dr. Robert Cook, of New York, spoke on the subject of "Allergic diseases". Another record was broken in the number attending the meeting and all enjoyed Dr. Cook's talk on a little understood subject.

Dr. Cook described the differences in allergy due to contact and those cases in which there seems to be a hereditary influence. Various infections also may be the sensitizing agent. The diseases of childhood are also sometimes suspected as the cause of a sensitization in allergy later in life. Sensitization may be induced by inhalation, ingestion, infection and injection. The sensitizing agent may not necessarily be protein. Examples of non-protein causative agents are aspirin and benzol derivatives. In some cases skin tests are of no value; in many cases the patient makes his own diagnosis, as in instances of sensitivity to clams. In some cases the skin reaction has no clinical significance, but these exceptional cases do not destroy the usefulness of skin tests. Dr. Cook discussed the frequency of asthma caused by aspirin, and spoke of the leucopenic index, which he has not found to be reliable. Dr. Cook really conducted a one-man round-table conference on the subject of allergy. At the close of the meeting, he answered a number of questions from the audience.

A. STANLEY KIRKLAND

Post-Graduate Courses

The Montreal Medico-Chirurgical Society

This Society extends a cordial invitation to all physicians in neighbouring communities to attend its Fifth Annual Clinical Convention, October 13 to 16, 1937.

October 13th, 9.00 a.m.—Registration

All non-resident Fellows and guests are requested to register. There is no registration fee.

9.30 a.m.—Program, Royal Victoria Hospital

Advantages of non-absorbable sutures. J. C. Luke.

Arthrodesis for tuberculous hip. W. G. Turner.
Treatment of ulcer of the lesser curvature by gastroplasty. J. C. Armour.

Urinary retention in children and adults. D. W. MacKenzie.

The use of bile salts in common duct obstruction. A. L. Wilkie.

Differential diagnosis of extra-hepatic obstructive jaundice. E. W. Archibald.

At 9.00 a.m., in the adjacent operating theatres, routine operative procedures will be performed by G. G. Miller and C. A. McIntosh.

A Buffet Luncheon will be served.

12 noon—Scientific Exhibit in Nurses' Home

2.00 p.m.—Montreal Neurological Institute

Protamine zinc insulin: successes and failures.

W. de M. Scriver.

The management of peptic ulcer. J. W. Macleod.

The thymus gland in infancy. G. Ross.

Endocrine preparations in clinical practice. J.

S. L. Browne.

Lessons from a case of prolonged chronic nephritis. D. S. Lewis.

"Athlete's foot" and allied fungus infections (with illustrative cases). L. P. Ereaux.

October 14th, 9.30 a.m.—Children's

Memorial Hospital

Poliomyelitis. H. B. Cushing.

After treatment of poliomyelitis. N. T. Williamson.

Infant feeding. A. Goldbloom.

X-ray demonstration. A. E. Childe.

Rheumatic conditions. R. R. Struthers.

Acute abdominal conditions. D. Ross.

Pneumonia in children. L. M. Lindsay.

Cleft palate. R. R. Fitzgerald.

2.00 p.m.—Montreal Neurological Institute

Surgical treatment of vascular hypertension.

W. G. Penfield and D. McEachern.

Clinical management of headache. F. McNaughton.

Psychogenic aspects in medicine; motion pictures. C. K. Russel.

Two cases of epilepsy relieved by craniotomy.

J. Saucier.

A case of brain cyst. F. H. MacKay.

Hypoglycæmic treatment of schizophrenia. G. E. Reed.

Management of hyperthermia in head injury.

T. I. Hoen.

Diet in the treatment of epilepsy. H. M. Keith.

October 15th, 9.30 a.m.—Montreal

General Hospital

Acne and its treatment. B. Usher.

(a) The "tidal" bladder irrigation (demonstration on case). K. T. MacFarlane.

(b) Gonorrhœa in the pre-adolescent female. D. W. Sparling.

Regional ileitis. F. Gurd.

Case of Pott's paraplegia. N. T. Williamson.

Infectious eczematoid dermatitis and its relation to focal infection. A review of a series of cases under investigation. J. F. Burgess.

Differential diagnosis between gall-bladder disease and coronary artery disease. A. H. Gordon.

Cataract operation: intra-capsular. R. J. Viger.

Renal colic. R. E. Powell.

Fracture of the femoral neck.

(a) The application of the Leadbetter manoeuvre for the reduction of fractures of the neck of the femur. H. G. Pretty.

(b) The use of stainless steel triradiate nail as an internal splint in the treatment of fracture of the neck of the femur (5 cases). R. R. Fitzgerald.

The treatment of acute nephritis in children, including that of the cerebral manifestations. A. Ross.

12.15 p.m.—Scientific Exhibit, Nurses' Home, Montreal General Hospital

A series of x-ray films illustrating lesions of the stomach and duodenum. W. L. Ritchie and staff.

A demonstration of neuropathic lesions of the vermiform appendix. J. E. Pritchard.

Demonstrations pertaining to blood transfusion: Practical demonstration of blood grouping and of a rapid test for exclusion of syphilis. Schematic representation of the technical steps in blood grouping (chart). Important points in selection of a blood donor (chart). L. J. Rhea and W. H. Mathews.

Demonstration of technical procedures in blood transfusions. C. K. P. Henry.

A series of paintings illustrating the blood picture in various blood diseases. E. S. Mills.

Graphic demonstration of results of a new method of treatment of diabetic coma. I. M. Rabinowitch and staff.

A series of ovarian tumours.

Microscopical slides of rare ovarian tumours.

Drawings illustrating the technique of vaginal hysterectomy. A. D. Campbell and staff.

2.30 p.m.—Montreal General Hospital

Regeneration of facial nerve. B. F. MacNaughton.

Ringworm infection of the feet. D. S. Mitchell.

Practical points in treatment of pernicious anæmia. E. S. Mills.

Toxicity of sulphanilamide. E. H. Bensley.

Some aspects of uterine bleeding. E. Percival and A. D. Campbell.

Treatment of severe bronchial asthma. H. E. MacDermot.

Gangrene and threatened gangrene of the foot. End-results of treatment by pavaex. H. M. Elder.

Case of double sciatica: pathology and treatment. J. A. Nutter.

Demonstration of neurological cases. F. H. MacKay.

October 16th, 8.30 a.m.—Royal Victoria Montreal Maternity Hospital

The following operative procedures will be demonstrated.

Suspension of uterus. G. C. Melhado.

Low Cæsarean section. H. C. Burgess.

Total hysterectomy. J. R. Goodall.

Repair of sacro-pubic hernia. J. R. Fraser.

Treatment of cancer (result of last ten years). W. A. G. Bauld.

Pathological exhibit of ovarian tumours. P. J. Kearns.

9.15 a.m.

Obstetrical anæsthesia. W. Bourne.

Feeding of the premature infant. A. K. Geddes.

Moving picture of a normal delivery as done in Royal Victoria Hospital. I. Y. Patrick.

Demonstration of normal delivery. A. D. Campbell.

Moving picture of a breech delivery. N. W. Philpott.

Obstetrical operation—forceps delivery. J. W. Duncan.

Study of uterine contractions before, during and following labour. J. S. Henry.

Syphilis of the placenta. P. J. Kearns.

On the afternoon of Saturday, October 16th, there will be an intercollegiate Football Game between Toronto Varsity and McGill, tickets for which will be available at the McGill Union.

Letters, Notes and Queries

"Vapo-Path"

To the Editor:

There is a patent preparation, of some kind, for rheumatism, called "Vapo-Path". It, of course, comes from the U.S.A. and its originator is "John F. Class". If you have any information about this treatment would you be so kind as to send it to me.

Yours sincerely,

Red Deer, Alta.

H. L. Nix.

August 16, 1937.

On this remedy the Bureau of Investigation of the American Medical Association has kindly furnished us with the following statement [Ed.].

"The John F. Class 'Vapo-Path' seems to be a new name for what used to be known as the 'John F. Class Health Fume System'. We have made no detailed analysis of the material said to be used by the Class concern, but we have made some cursory tests. From these it appears to be a creosote and naphthalene mixture. We have not, however, published anything on the thing.

"The John F. Class Health Fume System has been in existence for a good many years. The headquarters seem to be in Dayton, Ohio, while

the concern appears to have branches or agents scattered throughout the country. So far as we know, it is without scientific standing. Its 'treatment' has been variously known as the 'Health Fume System', the 'Mineral Fume Bath', and also as 'Hal-A-Fum', the latter being, apparently, a modification of the former, intended primarily for self-treatment.

"It has been claimed that the Class Health Fume 'permits the system to absorb through the pores and put into the blood those mineral elements which the body at the time may lack'. The thing is, apparently, recommended for whatever ails you.

"We might add that in April, 1934, the California Board of Medical Examiners started an investigation, the outcome of which we do not yet know, of the John F. Class scheme, after a Long Beach woman complained that her eardrums were permanently injured as a result of one of the Class 'baths'. She stated that the reason she took the treatment was because the Class people 'invited a group of our club members to come and hear their lecture and gave us \$5 for our club fund and a free ticket for a bath, as a means of advertising'."

What is the Best Treatment for Mycosis Fungoides?

A young medical man in Paris, France, has been the subject of a very acute attack of Mycosis fungoides. Treatment with x-ray and malaria has not produced any great benefit. He writes the *Journal* to know if any of our members can give him useful suggestions or could refer him to any pertinent articles on the subject in the literature. Any replies to his request will be transmitted to him by the *Journal*.—EDITOR.

Abstracts from Current Literature

Surgery

The Essential Features in Fractures of the Shoulder. Wilson, G. E., *Surg., Gyn. & Obst.*, 1937, 64: 347.

The era when fractures were treated by general practitioners has passed; they are being treated by surgeons interested in traumatic surgery. In order to get a more comprehensive understanding Wilson undertook some original investigations, the better to define the positions of the great and lesser tuberosities in six positions of the humerus. By placing fine wires around their borders he was able to exactly delineate their x-ray shadows. The first position was antero-posterior, arm by side with forearm pointing upwards, or forearm extended and

hand supinated; lesser tuberosity and neck well outlined. The second was the humerus internally rotated 30 degrees; lesser tuberosity well shown and great tuberosity moderately so. Third position, forearm across chest; both tuberosities well shown. Fourth position, full internal rotation (arm behind back); anatomical neck, head and great tuberosity clearly defined, with lesser tuberosity projecting medially as a cone-shaped mass. Fifth position, external rotation of 60 degrees; appearance much as in position 4. but reversed. Sixth position, internal rotation 60 degrees with flexion 30 degrees; head appears as a cyst-like mass occupying the full upper extremity; great tuberosity on lateral aspect and lesser tuberosity on medial aspect.

Further investigations were made of the movements of the proximal and distal fragments in transverse fractures of the surgical neck experimentally produced. The distal fragment could be moved freely in all directions except posteriorly to the proximal fragment (pectoralis major). The proximal fragment could be abducted, adducted and flexed with ease, but extension was difficult (infraspinatus and teres minor). Internal rotation occurred readily but external rotation required a very considerable twist (supraspinatus tendon of insertion and to a much less degree subscapularis, as division close to blending with capsule proved). With the proximal fragment abducted, flexed 30 degrees and internally rotated 60 degrees, cyst-like appearance is marked; great tuberosity projects about one-fourth inch above the head, and the lesser tuberosity is near inner margin of head. With the proximal fragment adducted 20 degrees, internally rotated and flexed, the head stands out behind and above the great tuberosity, the anterior margin of which extends vertically with cone-like projection of the lesser tuberosity to the inner side. With the proximal fragment abducted, extended 30 degrees and no rotation, the anatomical neck was clearly seen, the head pointed inwards, with a conical projection (great tuberosity) on the outer side.

The author reviewed 100 cases of fracture of the upper end of the humerus, most of which were transverse of the surgical neck. If the proximal fragment was abducted the shaft was usually to the outer side of the proximal fragment; if adducted, shaft was usually medial; if flexed, the shaft was usually anterior and with internal rotation was twice as often adducted. Flexion was present in 50 per cent and internal rotation in over one-third; the combination is a very common occurrence. Dr. Wilson treats these fractures by placing the shaft in alignment with the proximal fragment, with due regard to the advantages of some abduction in case of possible ankylosis, by plaster of Paris, and the use of fluoroscope and post-operative x-rays in two planes.

FRANK DORRANCE

A Radical Operation for Malignant Tumours of the Thyroid Gland. Crile, G. and Crile, G., Jr., *Surg., Gyn. & Obst.*, 1937, **64**: 927.

The authors bring forth a plea for a new surgical approach to lower prophylactically and therapeutically the mortality rate from malignancy of the thyroid gland. The malignant adenomas developing from benign solitary adenomas are five times more frequent than the papillary carcinomas developing in solitary adenomas, but both malignant tumours spread along the veins before they invade the capsule and metastasize by the lymphatics. In the diffuse adenomatous goitres prophylactic removal is not such a readily considered measure. The development of hardness in an adenoma is sufficient reason to advise removal within three months of its increase in size; fixation of an adenoma is evidence of capsule involvement. Lobectomy combined with ligation and excision as far distally as possible of the superior, lateral and inferior thyroid and internal jugular veins within three months of increased growth will usually prevent extension by the veins. With involvement of the capsule they advise implantation of radon seeds and deep x-ray therapy, following the above operative measures.

FRANK DORRANCE

Deformity of the Wrist following Resection of the Radial Head. Lewis, R. J. and Thibodeau, A. A., *Surg., Gyn. & Obst.*, 1937, **64**: 1079.

The authors call attention to a malalignment of the radio-carpal articulation which occurred within three years after removal of the head of the radius in 7 of 8 cases. The styloid process of the ulna lay on a transverse plane distal to the radial styloid process; widening of the joint occurred with instability of the inferior radio-ulnar articulation. In 2 of the 7 cases there was sufficient loss of function to prevent continuation of occupation. Loss of the growth centre in the head of the radius is probably of minor significance as a contributory factor. They suggest the formation of a new stabilizing position between the radial stump and the coronoid process.

FRANK DORRANCE

Obstetrics and Gynæcology

Notes from a Pregnancy Diagnosis Laboratory (1936). Crew, F. A. E., *Am. J. Obst. & Gyn.*, 1937, **33**: 989.

In 1936, 7,193 specimens were examined. Many more Aschheim-Zondek tests than Friedman tests were carried out. The laboratory offers a choice; it is the practitioner who decides. The Friedman test must necessarily be more expensive, and it would appear that in the majority of cases urgency is not a serious consideration; a report after five days is quite sufficient. Though the Friedman test in the

author's hands is undoubtedly the more delicate of the two, the Aschheim-Zondek is the more convenient procedure when very many tests are being carried out every day, and moreover the graded reactions that are obtained therein provide the means of distinguishing between several relative concentrations of the gondotropic hormones in different specimens, and permit us to refer to a strong positive, a rather weak positive, a weak positive, an extremely weak positive, a negative with uterine and vaginal enlargement in a variety of different conditions. Thus, a weak positive following upon a succession of strong positives in a case of habitual abortion permits us to warn the doctor that all may not be well. A weak positive in a case in which abortion is suspected to have occurred provides support for this diagnosis. A negative with vaginal and uterine enlargement at once raises the question as to the age of the patient.

The Friedman test is always used in cases in which medico-legal interest is concerned, and is followed by an Aschheim-Zondek. The combined Friedman and Aschheim-Zondek is the test that is to be preferred in the case of suspected ectopic gestation. Specimens from a series of ectopic gestation operated upon in the Edinburgh Royal Infirmary were examined. Specimens from 14 cases, taken within eight hours after the operation and thereafter daily for seven days, were tested, and in every case a definite negative test was invariably obtained seventy-two hours after removal of the embryo.

As in previous years, the errors are found to be concentrated at the beginning and at the end of the reproductive phase of life.

In those cases in which hydatidiform mole or chorionepithelioma is suspected, in addition to the ordinary Aschheim-Zondek in which prepared undiluted urine is used, groups of mice are injected with urine diluted with 9 and 99 times its own volume with distilled water. Experience has shown that while normal pregnancy can give a positive with undiluted urine and with the 1/10 dilution, it is exceedingly rare for it to do so with the 1/100; in fact so rare that a positive 1/100 is regarded as being strongly indicative of mole or chorionepithelioma.

ROSS MITCHELL

An Analysis of 521 Cases of Twin Pregnancy—Differences in Single and Double Ovum Twinning. Guttmacher, A. F., *Am. J. Obst. & Gyn.*, 1937, **34**: 76.

Monozygotic and dizygotic twinning represent fundamentally separate biological processes, as evidenced by differences in heredity, in the likelihood for recurrence, and in the influences of age and parity. Monozygotic twinning, true twinning or "twaining", appears to be a chance phenomenon, while dizygotic twinning, or the birth of a litter of two, seems to be regulated by special laws. The differentiation of twins into

two types seems to be equally satisfactory if done by a study of the fetal membranes or the physical comparison of the twins themselves months or years after birth.

ROSS MITCHELL

Temporary Postponement of Menstruation by Oestradiol Benzoate. Foss, G. L., *Brit. M. J.*, 1937, 2: 10.

Postponement of menstruation temporarily is occasionally justifiable, *e.g.*, when menstruation would coincide with weddings, examinations, or athletic championships. Inhibition of menstruation is simple by continuing therapy with 50,000 I.B.U. oestradiol benzoate throughout the cycle at intervals of three to four days. It is possible to postpone menstruation when injections are started, after ovulation has probably occurred, at about the nineteenth day of the cycle, but the dosage must be greater, such as 100,000 I.B.U., and the intervals should be shorter. There are no harmful effects. The technique of injection is of great importance.

ROSS MITCHELL

Urology

Renal Atrophy. Cumming, R. E. and Schroeder, C. F., *J. Urol.*, 1937, 37: 407.

The authors' interest in this subject was stimulated by the observation that certain kidneys for no apparent reason simply refused to carry on after apparent successful and routine operative interference. These conditions often go unrecognized until picked up by x-ray investigation. As a specifically new idea the authors believe that, even though the lesion in the diseased kidney appears to indicate an old infarct, the involvement may be actually due to the results of ascending infection with a nephro-fibrotic area corresponding to the units supplied by those particular vessels which are end-arteries. One reasonable basis for acquired atrophy and nephrofibrosis is that a peculiar renal status develops as a negative response to natural need; if one kidney has long carried the load of function its fellow gets no biological urge until sufficient disorder occurs to prevent appreciable recovery.

J. V. BERRY

Metastatic Pulsating Tumours of the Sternum Secondary to Renal Hypernephroma. Roth, L. J. and Davidson, H. B., *J. Urol.*, 1937, 37: 480.

Pulsating neoplasms of the sternum are of rare occurrence and more usually are secondary to hypernephromata or malignant adenomata of the thyroid. In a careful review of the literature, the authors present 5 cases of pulsating metastatic hypernephroma of the sternum. In the absence of aortic aneurysm and demonstrable neoplastic changes of the thyroid, a pulsating sternal mass should be strongly suspected as a metastatic hypernephroma, even though clinical evidence of a primary kidney

tumour is wanting. The inference made in regard to sternal metastases of carcinoma of the breast suggests that the tumours are not of a pulsating nature. Although the neoplasms apparently are solitary, the incidence of generalized metastases is unusually high and therefore surgical intervention is inadvisable.

J. V. BERRY

Neurology and Psychiatry

The Management of Fracture Dislocation of the Vertebrae Associated with Spinal Cord Injuries. Stookey, B., *Surg., Gyn. & Obst.*, 1937, 64: 407.

The lay public must be instructed that any injured patient unable to move arms or legs, or legs alone, should not be moved until competent help arrives. If the patient can move his arms, hands and fingers freely, but is unable to move his legs, he may be rolled over face downward, without lifting, on the presumption that the lesion is in the thoraco-lumbar region, and then transported; if both legs are paralyzed and the arms partially, he must be moved most cautiously by three or four persons, one pulling gently on the head and one likewise on the feet, not lifting, while the others carry him. Only by such careful handling can further damage be avoided. X-ray plates should be made as the patient is brought into the hospital and while still on the stretcher. Laminectomy is not justified except under exceptional circumstances. For fracture in cervical region with complete dislocation Taylor's method of reduction by controlled traction of the head with counter-traction of the lower extremities is advised. When fracture dislocations are incomplete, whether cervical or thoraco-lumbar, Stookey keeps the patient on an air mattress with hyper-extension at the indicated level. General supportive treatment in these cases includes unusually careful attention to all the small details of the care of the skin, bladder and bowels. The author describes a number of very practical points in regard to nursing care, the most striking of which is his suggestion of the use of acidophilus milk through the illness to minimize toxic absorption from the paralyzed gut.

FRANK TURNBULL

Therapeutics

Old Ununited Clavicular Fractures in the Adult. Berkheiser, E. J., *Surg., Gyn. & Obst.*, 1937, 64: 1064.

The author reports on 9 cases of non-union. Seven of these had to be subjected to open reduction. Six of them had signs of partial loss of function of the ulnar nerve. One had signs of impaired venous circulation. He has coined the term "costo-clavicular space" in order to describe the displacement of the fragments. There

is a distinct difference between the contents of this "space" in cadavera and in living subjects. He gives an x-ray technique which will show infringement on the space by fragments of clavicular fractures. Autogenous osteoperiosteal tibial bone grafts were used as inlay and onlay grafts for the clavicle. Rest on a hard bed with a snug-fitting Valpeau bandage was used for two weeks after operation. A plaster shoulder spica extending from the wrist to the iliac crests, with the elbow flexed to a right angle and with the arm in 45 degrees abduction, was then applied and retained for 10 weeks.

FRANK DORRANCE

Economic Advantages of Early Protected Weight-bearing in Fractures of the Leg, Foot and Ankle. Gurd, F. B., *Surg., Gyn. & Obst.*, 1937, 64: 1085.

The economic advantages referred to are, saving of much time in the early days of treatment if fracture is seen before swelling occurs, resumption of approximately normal activity in many cases before bony union has commenced, and a shorter period of time between receipt of injury and recovery of function following consolidation of the fracture. With the author's technique there is less swelling than with Delbet's splint, and there is the ability to have a shoe of good appearance and utility, which is not the case with Boehler's cast. The detailed technique of application of this cast, the post-reductive measures, and the construction of custom shoes are given.

FRANK DORRANCE

Pathology and Experimental Medicine

Magnesium Metabolism in Health and Disease.

I. The Magnesium and Calcium Excretion of Normal Individuals, also the Effects of Magnesium Chloride and Phosphate Ions. Tibbetts, D. M. and Aub, J. C., *J. Clin. Invest.*, 1937, 16: 491.

Much attention has been paid in recent years to the subject of inorganic salt metabolism. Great advances in our knowledge have been made in regard to the exchange of calcium and sodium, but a surprising ignorance exists in the matter of magnesium exchange. Magnesium is obviously an important constituent of the body. In spite of a fairly close relationship, chemically speaking, between calcium and magnesium their distribution in the body is widely different, which fact would make one anticipate that their physiological actions are of different natures. Physiological evidence shows that, sometimes at least, their effects are antagonistic. It is therefore of interest to discover whether the influences which affect calcium metabolism have analogous effects upon the exchange of magnesium.

The authors found that magnesium balance was obtained with hospital patients on an intake

of 220 mg. per day, and magnesium storage in active subjects on 300 mg. per day. There was a parallelism between calcium and magnesium metabolism in response to the ingestion of NH_4Cl and both inorganic and organic phosphates. The changes, however, in magnesium metabolism were of much less magnitude than were those of calcium, but they were larger than could be accounted for by the amount of magnesium in bone. From this it is apparent that an entire cellular cation can be used for neutralizing excess acid ions in urine. Increased ingestion of magnesium lactate resulted in an increase in the urinary excretion of calcium, a response which was checked by a large intake of sodium acid phosphate. Magnesium lactate accentuated the effect of ammonium chloride in elevating urinary calcium excretion. It is therefore clear that the ingestion of magnesium increases the elimination of calcium.

JOHN NICHOLLS

Magnesium Metabolism in Health and Disease.

II. The Effect of the Parathyroid Hormone. Tibbetts, D. M. and Aub, J. C., *J. Clin. Invest.*, 1937, 16: 503.

Observation of patients in the hyperparathyroid state, both before and after operation, gave some interesting results. The excretion of magnesium in the hyperparathyroid state is essentially at a normal level, and two out of three cases stored more magnesium than did the normal controls. Correcting the hyperparathyroid condition is followed, however, by a temporary fall in the excretion of magnesium, particularly in the urine. A few months after parathyroidectomy the excretion of magnesium returns to its level before operation, while calcium retention remains intense. Administration of parathyroid extract temporarily raises the excretion of urinary magnesium to a degree that indicates that some of it is derived from soft tissue. The magnesium excretion appears to be independent of changes in the intake of calcium in hyperthyroidism. The addition of magnesium gluconate to the diet does not relieve the drain upon body calcium due to the hyperthyroidism, as would the administration of calcium. The reverse is true, because increased ingestion of magnesium increased the excretion of calcium. Although magnesium is not substituted for calcium in the excretion during hyperthyroidism, the storage of magnesium suggests that it may possibly substitute for calcium in the bones.

JOHN NICHOLLS

Magnesium Metabolism in Health and Disease.

III. In Exophthalmic Goitre, Basophilic Adenoma, Addison's Disease and Steatorrhoea. Tibbetts, D. M. and Aub, J. C., *J. Clin. Invest.*, 1937, 16: 511.

These observations record the study of four

diseases in which the metabolism of several inorganic elements is markedly influenced.

Exophthalmic goitre shows a considerable elevation of calcium excretion without change in the blood level. A case of Cushing's syndrome also showed a great loss of calcium before treatment, which changed to a less than normal excretion after the disappearance of the disease.

Addison's disease shows a high excretion of sodium chloride, which is so large that it is accompanied by an extensive fall of these ions in the blood serum. However, none of these abnormalities in which a fundamental change in inorganic salt metabolism is involved has much effect on the metabolism of magnesium. In all of these conditions the excretion of magnesium is a little lower than in the normal controls, and in pituitary basophilism it remains unchanged in the two observations made, in spite of the marked changes in the excretion of calcium.

Also, in a patient with steatorrhœa, where calcium is absorbed with sufficient difficulty so that a low blood calcium and tetany result, one finds no fundamental abnormality in the excretion of magnesium.

The extreme specificity of these effects is interesting. One would expect some reciprocal relationship in an organism in which electrolyte levels are so closely guarded. No such influence, however, is apparent in these observations. Thus, we have a situation of two cations, closely related chemically, which behave quite independently in the body. Magnesium, essentially a constituent of cells, may be but little influenced by the factors which effect calcium excretion. Indeed, the rate of excretion is remarkably constant in all the subjects whom the authors studied. Therefore one must conclude that the usual assumption that calcium, magnesium, and phosphorus necessarily respond as a group is unjustified.

JOHN NICHOLLS

Anæsthesia

Rectal Basal Evipal Anæsthesia. McNellis, P. J., *Current Res. in Anæst. & Anal.*, 1937, 16: 193.

Following the technique proposed by Gwathmey, the author has employed rectal evipal as a basal anæsthetic. The dosage employed is 0.02 g. (or 0.2 c.c. of a 100 per cent solution) per pound of body weight for the average patient in good health. The dosage is calculated by taking the weight of the patient and multiplying it by 0.02, viz.: for a patient weighing 100 lbs., 2 g. of evipal soluble are required ($100 \times 0.02 = 2.0$). This amount of the powder is dissolved in 30 c.c. of distilled water and injected into the rectum, taking about five minutes for

the instillation. The patient falls asleep in from ten to twenty minutes. When narcosis is complete he is conveyed to the operating room when the supplemental anæsthesia is commenced.

The advantages of this form of basal anæsthesia over others currently in vogue are several. There is practically no change in respirations, pulse rate, or blood pressure. The frequently associated effects of a general anæsthetic, such as restlessness, vomiting and headache are decreased as less inhalational anæsthetic is required; psychic trauma is diminished and there is less need for post-operative sedatives. It has also been found that rectal evipal is useful in the control of acute alcoholism associated with excitement. The small volume employed obviates the feeling of fullness in the rectum frequently complained of when other rectally administered anæsthetics are given.

F. ARTHUR H. WILKINSON

Hygiene and Public Health

The Declining Mortality from Chronic Nephritis. *Statistical Bull., Metropolitan Life Ins. Co.*, 1937, 18: 5.

A steady and impressive decrease in the death rate from chronic nephritis is one of the outstanding features of the mortality situation in recent years. Among the industrial policyholders of the Metropolitan Life Insurance Company the death rate from chronic nephritis in 1936 was 51.4 per 100,000, as compared with 109.1 in 1911. Part of this decline is probably genuine, part is only apparent and is probably due to a change in the interpretation of the clinical picture in older persons dying of arteriosclerotic and hypertensive disease in which the kidneys, the heart and the vascular system are all involved. Part of the genuine decline may be attributed to a lesser incidence of communicable diseases and part to an improved nursing and therapeutic technique for these diseases. Improvement in pre-natal care may have contributed somewhat, as possibly has the decline in the birth rate itself. In various ways, and largely because of the greater frequency of physical examinations, many cases of nephritis are discovered early when most can be done for the patient. In retarding or postponing deaths the death rate is thereby lowered. It is difficult to determine what percentage of this decline is real and what percentage is due to a change in diagnosis.

FRANK G. PEDLEY

Infant Mortality in New York City. Rice, J. L. *et al.*, *Am. J. Pub. Health*, 1937, 27: 701.

In common with other cities in the United States and abroad New York has experienced a marked decline in its infant mortality rate during the past twenty years. The rate has declined from 93 per 1,000 live births in 1916 to 48 in 1935. The general trend in the decline,

however, has not been the same for all causes. The greatest progress has been made in those fields where knowledge has been the greatest—deaths from diarrhoea, and deaths from certain communicable diseases, such as measles, scarlet fever and whooping-cough, deaths from respiratory diseases show a very modest decline, and deaths from congenital causes and early infancy show an almost stationary level. Many factors undoubtedly contribute to the decline in infant mortality. The regular health supervision of the infant and the education of the mother in the care and feeding of the baby, the safeguarding of the milk supply, the control of communicable diseases, and the general health education of the public have all played an important part in improving the health of infants. During the depression the restriction of emigration and the closer supervision of a large part of the population on relief have been additional factors. The next steps in the infant health program, it would appear, should be directed towards the very young infant, the mortality among which has not declined appreciably. To this end the New York City Health Department, through its new plan of decentralization into 30 health districts, will conduct a more intensive program in behalf of very young infants. In the districts first organized the registration of infants under one month of age has increased by more than 50 per cent. An Advisory Obstetrical Council of 18 leading obstetricians has been appointed to study the problem of neo-natal mortality. One of the recommendations of the Council is that every physician in a pre-natal clinic must have affiliation with the obstetrical staff of a recognized hospital. Increased emphasis is being laid upon the diagnosis and treatment of syphilis in pregnancy. Wassermann tests are taken on all women attending public pre-natal clinics, and facilities are now available for adequate treatment. Prematurity is one of the most important of neo-natal deaths and a large use of available incubators, etc., is being encouraged. The Mothers' Milk Bureau is carrying on a valuable work in behalf of premature infants.

FRANK G. PEDLEY

Obituaries

Dr. A. Boak Alexander died in the Winnipeg General Hospital on September 3, 1937, less than four months after he had retired as medical superintendent of the Municipal Hospitals. He was born in Nova Scotia in 1872 and received part of his education in Dalhousie University at Halifax. In 1889 he came to Winnipeg, graduated in Arts from the University of Manitoba in 1893 and in Medicine in 1897. He practised for ten years in Killarney, then returned to Winnipeg, where he engaged in private practice until 1911 when he became superintendent of the city hospitals.

Dr. Herbert Leslie Barber, of Toronto, died suddenly on August 21, 1937, in his seventy-first year.

Dr. Barber was born at Roche's Point, graduated a silver medallist from Trinity University in 1892, and practised in Burk's Falls until 1928, when he retired and came to Toronto to live. He always took an active interest in public life, served on school boards and on Board of Trade committees. He was formerly Coroner and Medical Officer of Health.

Dr. Denis J. H. Berthiaume, of Montreal, died on August 24, 1937, in his seventieth year. Born at St. Marthe, Que., he was the son of Moise Berthiaume and Mary Kennedy. He completed his classical studies at Rigaud College and graduated in Medicine from Victoria University, Cobourg, Ont. (1890). He practised in Montreal for the past twenty years.

Dr. Wilber Franklin Brown, of St. Mary's, Ont., died on August 14, 1937. He was born in Brown's Corners, East Nissouri, in 1862, the son of Mr. and Mrs. Elisha Harris Brown, and after teaching school in Medina and at McKim's school house, entered the University of Toronto Medical School. On graduation in 1893 he settled in St. Mary's. After 34 years of active practice, Dr. Brown retired in 1927.

Dr. John Lewis Day, of Westmount, Que., died on September 12, 1937, after a lingering illness. He was in his seventieth year. After passing through the Montreal High School, there taking the gold medal of his year, Dr. Day took his Arts course at McGill University, winning the Davidson Gold Medal in Classics in 1888. He then took a position in the Arts Faculty and rapidly gained a reputation as a teacher and a scholar. In 1891 he began to attend the courses in the Medical Faculty of McGill University, at the same time continuing to hold his position as Lecturer in Classics in the Arts Faculty. He took his M.A. degree in 1895 and his M.D., C.M. in the same year. After graduation, Dr. Day obtained a position on the staff of the post-graduate hospital in New York. Returning to Montreal, Dr. Day began practice and soon became connected with the Montreal Dispensary where he rapidly built up a large clinic. Of late years Dr. Day had not been in active practice.

Always an ardent book-lover, his library, the nucleus of which came from his grandfather, the late J. J. Day, Q.C., contains much that is not replaceable, his Canadiana being particularly numerous and valuable. Dr. Day is survived by his widow, formerly Gertrude Thompson, of Toronto, and by two brothers, Maurice Beldin and Albert Jessup Day, both of Montreal.

Dr. Roy John Farmer, of Toronto, died suddenly on August 25, 1937, aged fifty-one. Dr. Farmer was born in London, Ont., the son of the late John Farmer. He graduated in Medicine at the University of Western Ontario (1916), and moved to Toronto in 1920. A veteran of the Great War, Dr. Farmer went overseas with the 34th Battalion in 1914, but was later transferred to the Royal Navy, where he rose to the rank of lieutenant.

Dr. Frederick S. Greenwood, of St. Catharines, Ont., died on August 4, 1937, in his eightieth year. Born in St. Catharines he was a son of the late William and Eleanor Stowell Greenwood, of Keighley, Yorkshire, England.

Dr. Greenwood received his early education in St. Catharines, and, after attending Grantham Academy, went to McGill University, where he graduated with the degree of M.D. in 1878. He then went to England for a year's post-graduate work. In 1879 he received the diploma of L.R.C.P. at St. Thomas Hospital, London. Returning to St. Catharines, he prac-

tised with the late Dr. Theophilus Mack and took over his practice when Dr. Mack died in 1881.

Dr. John Nisbet Gunn, of Calgary, Alta., died on August 26, 1937, aged fifty-eight. Dr. Gunn was born in Beaverton, Ont., and was educated in Ontario, taking his medical training at the University of Toronto (M.B., 1902). In 1903 he obtained the diplomas of L.R.C.P.(Lond.) and M.R.C.S.(Eng.). He came to Calgary in 1907, and had lived there ever since, specializing in ophthalmology.

During the war Dr. Gunn saw active service with the rank of colonel in the 8th Field Ambulance Brigade. He headed a Canadian Army Medical Corps draft which left Calgary in 1915 for France. He was awarded the D.S.O. for his services.

Dr. Frederick Samuel Harper, of Hamilton, Ont., died on June 15, 1937. He was a graduate of the University of Toronto (1910).

Dr. Andrew Jerome Harrington, of Toronto, life Fellow of the Academy of Medicine and life member of the Ontario Medical Association, died on August 5, 1937. Dr. Harrington was born in Lindsay, Ont., on June 24, 1861. He was educated at the Port Perry High School, the Ontario School of Pharmacy, where he won the Rose gold medal, and at Victoria University, Cobourg (M.D., C.M., 1889). He spent a year studying in London, Edinburgh and Paris, and obtained the membership of the Royal College of Surgeons, London, in 1890. He settled in Toronto in 1891.

Dr. Archibald Jamieson, of Arnprior, Ont., died on August 19, 1937. He was a graduate of Queen's University (1886), and L.S.A.(Lond.) (1887).

Dr. George Bertie Kennedy, of Seabright, N.S., died on September 9, 1937. He was sixty-two years of age. Dr. Kennedy was the son of the late Rev. and Mrs. John Kennedy, and a graduate of the University of Western Ontario (1901). He served four years overseas with the Canadian Army Medical Corps, and he practised in New Germany, Tangier and Elmsdale, N.S., before establishing himself at Seabright.

Dr. Richard Turnbull Kidd, of Atwood, Ont., was accidentally drowned at Bruce Beach, near Kincardine, on August 15, 1937. He was thirty-two years of age, the son of the late Mr. Richard Kidd and of Mrs. Kidd, Listowel, and a graduate of the University of Western Ontario (1931).

Dr. Alexander W. Miller, of New Waterford, N.S., died on September 11, 1937. He was born at Margaree Forks in 1869, the son of Mr. and Mrs. Joseph Miller, and went to the county school in that community. Later he worked his way through college, graduating from St. Francis Xavier University and then receiving his degree in medicine at Dalhousie University (1905).

Dr. John J. Moore, of Brooklin, Ont., died on August 11, 1937, in his seventy-fifth year. He was born in Reach Township, the son of Mr. and Mrs. Allan Moore, pioneers in that district. Graduating from Port Perry High School, Dr. Moore attended Trinity Medical School (M.D., C.M., 1891). In 1891 he came to Brooklin, where he had resided ever since. At one time he was Reeve of Whitby Township.

Dr. James Freeborn McKee, of Thornbury, Ont., died on August 26, 1937. He was a graduate of the University of Toronto (1906).

News Items

Alberta

An opening exists in the City of Edmonton for a graduate physician who is holder of special public health qualifications to fill the post of medical officer of health which falls vacant October 8, 1937.

From January 1, 1928, until August 31, 1937, a period almost of ten years, the College of Physicians and Surgeons of Alberta has registered 298 medical practitioners, 180 of whom graduated from the University of Alberta, and 178 from other universities, mostly Canadian; all grade A. however. During that period Alberta University graduated 230 physicians, many of whom were domiciled outside Alberta and consequently registered elsewhere. Of the 120 who did register only 75 are still in this Province.

Lacombe, a town 120 miles north of Calgary, has just laid the corner stone of their new community hospital. The new hospital will have 30 beds and is being backed by the rural adjacent districts as well as the town. The former hospital which was smaller and purely a town proposition will be used for other purposes. Coins of 1937, together with coronation medals of King George VI and Queen Elizabeth, and a copy of the local paper, *The Globe*, were deposited by Mayor Jones in a copper receptacle.

The President-elect of the Canadian Medical Association, Alberta Division, Dr. J. K. Mulloy, is quite air-minded, and took a plane to attend the meeting of the Peace River District Medical Association which was held on August 25th at Dunvegan, when after the scientific program, a sports picnic and banquet were held. The clinicians accompanying Dr. Malloy were Drs. J. W. Scott and Eardley Allin, of Edmonton.

The mining town of Canmore is to have a new hospital. The residents are donating free labour estimated at \$5,000. The Coal Company is loaning \$5,000, in addition to paying half the cost of the building. The town families looking for medical care and hospitalization on a monthly cost basis are reported to have agreed to pay \$3.00 monthly.

The following are new registrants in Alberta since July 1, 1937: Maurice Yoachim, William M. Toone, Frederick Pilcher, Alan F. McGill, Reuben E. Jespersen, Lorne A. Archibald, Arthur S. McConkey, William A. Doidge, J. Tenbrooke MacLean, S. F. Carr, George MacKay, L. H. Webster, A. W. Hardy, G. N. Tucker.

The various committees of the Canadian Medical Association, Alberta Division, are presenting their annual reports to the Convention in which they regret that no provision is yet made to provide a fund for the hospitalization and medical care of victims of motor accidents. In most cases the victims are without means, and the physicians and hospitals scarcely get a "thank you". A plan is on foot to prepare a formulary for use in prescribing, thus assisting the pharmacist in limiting the variety of the stock he carries and assuring the physician that the patient gets the remedy he intends him to have.

The Maternal Welfare Committee, in viewing the mortality of pregnant women, have come to the following conclusions: (1) women must be urged to con-

At the menopause

EMMENIN THERAPY FOR THE CONTROL OF SUBJECTIVE AND OBJECTIVE SYMPTOMS

- The fact that Emmenin is orally-active has been demonstrated by several workers.^{1, 2, 3, 4} In a recent report by Salmon and Frank⁵ on a small series of cases suffering from disturbances of the menopause, spontaneous and castrate, the efficacy of Emmenin was again confirmed. The subjective symptoms (flushes, sweats, headaches, neurovascular symptoms, digestive disturbances) showed a gratifying response to Emmenin therapy.
- In addition, it was shown that Emmenin, through (it is presumed) its inhibitory action on the hypophysis, caused the disappearance of the gonadotropic hormone present in the urine of the patients in the series, coincidentally with the alleviation of the subjective symptoms.
- From the above report, as well as other clinical reports regarding the use of Emmenin at the menopause, we feel justified in again bringing Emmenin to the attention of the medical profession for the treatment of this distressing condition.

EMMENIN » » » the water-soluble, orally-active, oestrogenic placental hormone is prepared and standardized after the technique of Dr. J. B. Collip and supplied with the approval of the Department of Biochemistry, McGill University.

Emmenin Liquid—in original 4-oz. bottles.

Emmenin Tablets—in bottles of 42.

1. Goldberg, M. B., and Lissner, Hans—*Endocrinology* 19: 649 (December) 1935.
2. Atkinson, A. J., and Ivy, A. C.—*J. Amer. Med. Ass.* 106: 515 (February 15) 1936.
3. Macfarlane, Catharine—*Amer. J. Obstet. Gynec.* 31: 663 (April) 1936.
4. Schneider, P. F.—*Amer. J. Obstet. Gynec.* 31: 782 (May) 1936.
5. Salmon, Udall J., and Frank, Robert T.—*Endocrinology* 21: 476 (July) 1937.

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MONTREAL

CANADA

sult their physicians early and regularly; (2) major obstetrical procedures, unless emergent, should be performed in adequately equipped hospitals only; (3) a further and more intensive survey should be made for next year with cooperation of all of the Alberta profession.

The Committee on Legislation is recommending a further study of the question of a practical Alberta Basic Science Law, also a clarifying of the Municipal Districts Act, as to what constitutes an indigent, and what a physician may do in an emergency without a written order.

G. E. LEARMONTH

British Columbia

According to the statement of Dr. C. M. Hincks, of Toronto, General Director of the National Committee for Mental Hygiene of Canada, British Columbia leads the rest of Canada in post-graduate training of psychiatrists and is making splendid progress in extension of out-patient clinical services and provision of mental hygiene training for nurses. Dr. Hincks has been visiting British Columbia for the purpose of conferring with provincial officials on treatment of mental disorders.

An addition to the Prince Rupert Hospital, which will include a heating system with four-bed, two-bed, and single bed rooms and a new elevator, is being contemplated by the Board of Directors. Mr. H. Whittaker, provincial architect, will make a survey and computation of the cost of the new structure in the immediate future.

Work has commenced on the new residence for interns at the Vancouver General Hospital. The building will be across the street from the main building of the hospital. Landscaping and re-arrangement of roadways to accommodate and enhance the appearance of the newer units of the hospital, including the Institute for Diseases of the Chest with its recently added wing, are now complete.

The North Pacific Society of Internal Medicine held its fall meeting in Victoria on September 3rd and 4th under the presidency of Dr. Downing, of Portland, Ore. Drs. Stuart G. Kenning and D. M. Baillie are the Victoria members of the Society. Among those who addressed the Association from Vancouver were Drs. Frank Turnbull, Bede Harrison, and C. E. Dolman. Dr. Edwin G. Bannick, of Rochester, Minn., was the principal speaker, his papers dealing with nephritis, blood sedimentation tests, and sulphanilamide therapy. Golf was played at Oak Bay and Colwood courses on the afternoon of September 3rd and 4th.

D. E. H. CLEVELAND

Manitoba

On August 26th a reception was held at the Manitoba Club in honour of Dr. William Boyd, Professor of Pathology, who leaves to assume a similar position in the University of Toronto. In addition to a large number of medical men, President Sidney Smith, of the University of Manitoba, Mr. C. A. Adamson, a Governor of the University, Mr. John McEachern, Mr. A. E. Johnston, K.C., Mr. Harry Ashdown, representing the Trustees of the Winnipeg General Hospital, Lt.-Col. H. F. Osler, and other laymen were present. Dr. J. D. McQueen, Chairman of the Honorary Attending Staff of the Winnipeg General Hospital, and Dr. A. T. Mathers, Dean of the Faculty of Medicine, expressed their regret at Dr. Boyd's departure from Winnipeg after twenty-one years' of service and wished him godspeed in his new field of labour. Dr. Mathers stated that the Medical Faculty Executive Council had decided that the

pathological museum should henceforth be called the "Boyd Museum of Pathology" since Dr. Boyd had made it the unique thing it is.

A presentation was then made of a silver tea service suitably engraved. As Dr. Boyd was temporarily indisposed by an attack of laryngitis Dr. W. A. Gardner responded for him as "the voice of William Boyd", but at the close Dr. Boyd was able to say a few words in which he stated that Winnipeg would always seem to be his home.

Dr. Stephen B. Thorson, who has been assisting Dr. William Boyd in the Department of Pathology, Winnipeg General Hospital, will leave shortly to assume a position in the Department of Pathology, Tufts College Medical School, Boston, Mass.

The pensions for the blind became effective on September 1st in Manitoba with the proclamation of the legislation passed by the province in 1935 and by the Parliament of Canada in 1937. Two hundred blind persons in the province will be eligible for the first payments, the maximum of which is \$20.00 a month. Pensions are to be paid to blind persons of 40 years of age or over, subject to a schedule of reduction in cases of other sources of income. The terms of this are substantially the same as the reduction set out in the Old Age Pensions Act. The Manitoba Pensions Act will be administered by the Old Age Pensions Board. The proportion paid by the two governments is 25 per cent by the province and 75 per cent by the Dominion. The province's share for the current year is estimated at \$12,000 and this amount was voted by the legislature last winter.

ROSS MITCHELL

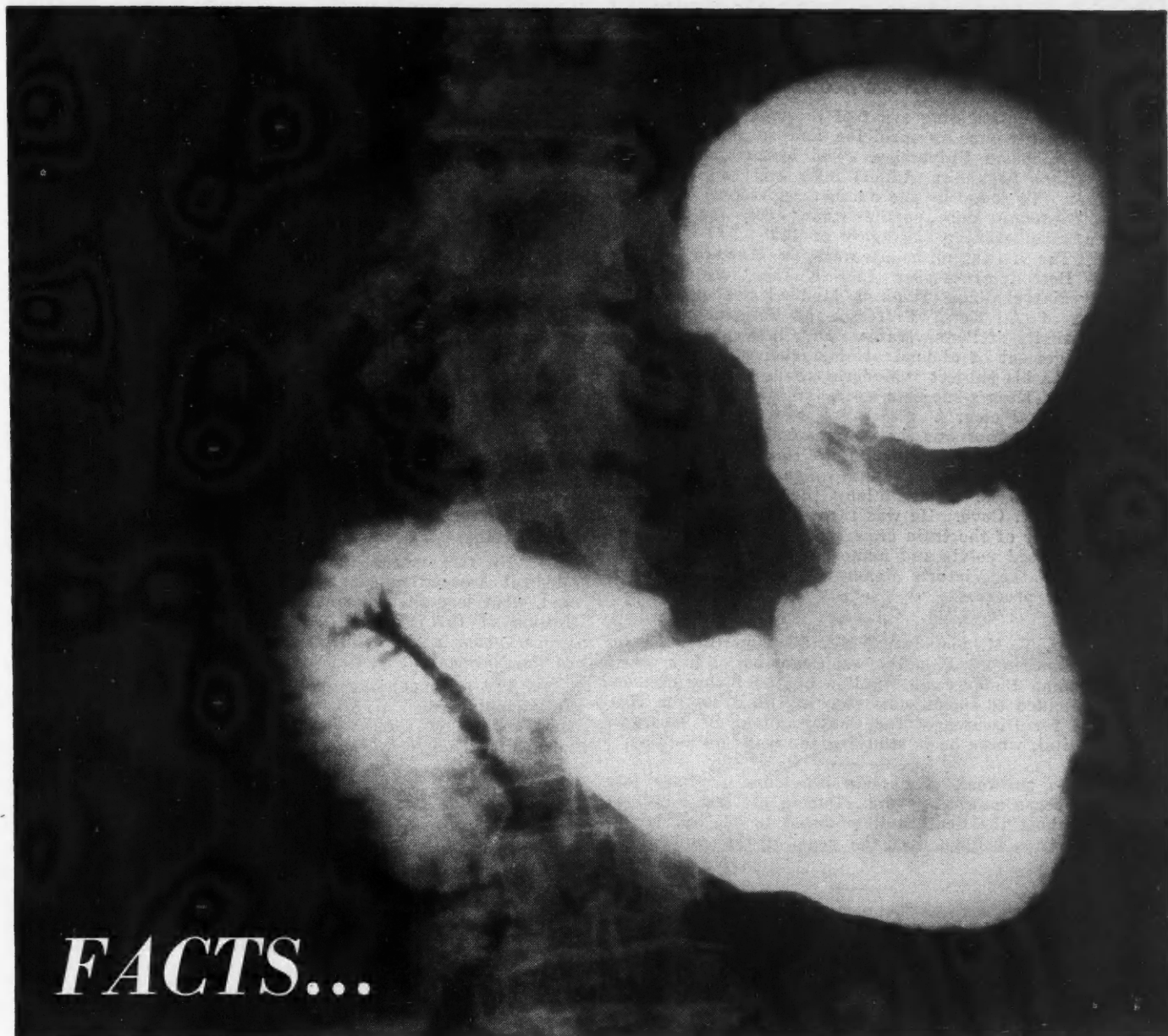
New Brunswick

During the past few weeks a considerable number of cases of poliomyelitis have developed in New Brunswick. The disease has been fairly widespread throughout the district. So far there have been 2 deaths and 7 cases of paralysis. The Department of Health has issued orders forbidding the re-opening of schools until further notice, and banning other meetings of children. The Department has also been able to accumulate and provide convalescent serum for depots throughout the province sufficient to meet local demands. Dr. William Warwick, Chief Medical Officer of Health, and his staff have had excellent support from the physicians of the province and from the Government in handling the present epidemic.

The Department of Health for the Province of New Brunswick advises that under new organization the province will in future be divided into health districts, with the following health officers in charge at the mentioned headquarters: Madawaska—Dr. J. P. Richard, at Edmundston; Restigouche—Dr. R. Monahan, at Campbellton; Gloucester—Dr. J. E. Paulin, at Tracadie; Northumberland—Dr. W. S. Loggie, at Chatham; Kent—Dr. G. C. Leger, at Buctouche; Westmorland-Albert—Dr. J. A. Melanson, at Moncton; Kings-Queen—Dr. H. L. Logan, at Sussex; Saint John-Charlotte—Dr. C. W. MacMillan, at Saint John; Fredericton-York-Sunbury—Dr. J. M. Cameron, at Fredericton; Carleton-Victoria—Dr. A. M. Clark, at Woodstock.

The Saint John Medical Society tendered a complimentary dinner to Dr. Norman Skinner whose marriage took place on the first of September.

A. STANLEY KIRKLAND



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LESS than thirty years ago the diagnosis of malignant disease in regions not readily accessible to visual or manual examination was practically restricted to its late, obvious stages. But today you are not in that helpless position. . . . Instead, you have at your command a dependable diagnostic medium—radiography.

This is particularly important when carcinoma of the esophagus, stomach, small intestine, or colon is a possibility. Statistics show that approximately 50% of all fatal malignancies occur in the digestive tract, and that physical or clinical diagnostic measures are of little value

in their early recognition. Radiography, however, has a high percentage of accuracy—at least 95% in cancer of the stomach.

Since early diagnosis is the prime essential in the fight against cancer, the radiological specialist is your most important ally. His radiographs and observations can provide the earliest conclusive diagnostic information . . . determine the location, extent, and probable character of the new growth . . . furnish invaluable indications as to the most effective therapeutic measures. Canadian Kodak Co., Limited, Toronto, Ontario.

RADIOGRAPHS PROVIDE DIAGNOSTIC FACTS

Nova Scotia

The outstanding event of the month was the 16th refresher course in medicine and surgery, sponsored by Dalhousie University. The lectures and demonstrations began on August 30th and lasted for one week. To judge by the number registered, the course is becoming more popular than ever, the total attendance reaching the figure of 142.

The visiting clinicians were, Dr. Howard M. Clute, of Boston; Professor Leo Kanner, Professor of Psychiatry, Johns Hopkins Medical School, and Dr. Richard A. Kern, Professor of Clinical Medicine, University of Pennsylvania. Dr. Clute spoke on "The management of abdominal emergencies"; Dr. Kanner took as his subject "Modern trends in psychiatry"; and Dr. Kern's subjects were, "Clinical allergy" and "Duodenal ulcer".

Dr. Kanner was the victim of a most unfortunate accident. He was returning to Halifax from a visit to the Nova Scotia Hospital when he was struck by a train as he walked along the railway trestle at Dartmouth Cove. He was thrown into the water, but a member of the train crew rescued him. He suffered a fractured pelvis and numerous bruises. He is confined to the Victoria General Hospital, where he is making progress.

Dr. T. M. Sieniewicz, Medical Superintendent of the Tuberculosis Hospital, was a member of this year's Canadian Bisley team. Following the Bisley matches he decided to spend some time at the Brompton Hospital for Diseases of the Chest, and at St. George's Hospital, where he is studying the work on asthma.

An outbreak of cholera infantum in Glace Bay has been somewhat severe. During the last fortnight of August the death toll mounted to 11, but health authorities believe that the peak of the epidemic is over.

N. B. DREYER

Ontario

The President of the University of Toronto announces that Lady Eaton and the T. Eaton Company have extended for another five years their gift of \$25,000 a year to the Department of Medicine and the Faculty of Medicine. It is nineteen years since Sir John and Lady Eaton undertook to support the funds for the Sir John and Lady Eaton Chair of Medicine in the University. The funds have not only supported a full-time Professor of Medicine but have provided for research in the Department of Medicine. This gift has been in part responsible for the great development of the Department of Paediatrics within the University.

J. H. ELLIOTT

Quebec

The following circular letter has been sent to all members of the English-speaking medical profession in the Province of Quebec. It speaks for itself.

"The Province of Quebec Medical Association has ceased to function for at least two years, and particularly as an affiliated Branch of the Canadian Medical Association.

"As a result, the members of the Canadian Medical Association resident in the Province of Quebec no longer secure proper representation on the Council or Executive Committee of the Canadian Medical Association. Under these circumstances it is obvious that those of us who desire to continue in affiliation with the Canadian Medical Association and to take part in its activities to mutual advantage must form a new body through which this franchise may be exercised.

"The undersigned organization committee suggests that steps be taken to form an organization in this

Province which shall become the Canadian Medical Association, Quebec Division.

"Under the new Constitution of the Canadian Medical Association, Provincial Medical Organizations may become 'Divisions' of the Canadian Medical Association. Membership in a Division automatically carries membership in the National Body, with all the privileges of membership, including the *Journal*.

"The composite fee for membership in a Division and the Canadian Medical Association is \$10.00, \$8.00 of which goes to the Canadian Medical Association, leaving \$2.00 available for the expenses of the Division.

"A Division elects its own representatives to the Council and to the Executive Committee of the Canadian Medical Association, and also participates in all activities of the Canadian Medical Association through membership on Standing and Special Committees.

"There are about 350 members of the Canadian Medical Association resident in the Province of Quebec. If all of these will agree to the proposed arrangement the suggested close relationship with the Canadian Medical Association may be maintained. It is confidently expected that many recruits can be added to the present membership.

"By this means the influence of the Canadian Medical Association can be extended in this Province and, what is perhaps more important, the medical profession of this Province will be enabled to take its proper place in the deliberations, decisions and actions of the National Body.

"The accompanying questionnaire is being sent to all Canadian Medical Association members resident in the Province of Quebec and to others who should be members.

"It is proposed to call a general organization meeting of those approving the plan during the Clinical Convention of the Montreal Medico-Chirurgical Society to be held in Montreal in October next.

"Please reply promptly in the enclosed stamped envelope in order that action may not be delayed.

Yours truly,

A. T. BAZIN, D. S. LEWIS, J. C. MEAKINS, F. S. PATCH, H. R. CLOUSTON, W. H. DELANEY, G. F. L. FULLER, W. W. LYNCH.

*Organization Committee,
Canadian Medical Association, Quebec Division."*

Dr. Edward W. Archibald, Professor of surgery and Director of the Department of Surgery, McGill University Faculty of Medicine, Montreal, was presented with the Henry Jacob Bigelow Medal of the Boston Surgical Society, May 21st, at the Boston Medical Library, Dr. William C. Quinby, of Boston, president of the Society, made the presentation, and Dr. Archibald spoke on "French surgery in the first half of the nineteenth century". Under the will of William Sturgis Bigelow, in memory of his father, a sum of money was presented to the Society, "the income of which is to be used from time to time for the presentation of a gold medal to some outstanding surgeon for his work in the advancement of the science of surgery".

United States

The American Board of Surgery.—We learn that this Board is now functioning and held its first examination (Part I, written) on September 20, 1937. This Board is a member of the Advisory Board of Medical Specialties, which includes all of the boards of certification for the different medical specialties which have been already organized. It will be responsible for the certification of general surgeons as well as those practising in the specialized subdivisions of surgery.

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Prescribe Angier's as a therapeutic agent when these cases start their annual colds and coughs—it will abort or shorten the course. Prescribe it as a tonic and regulator—and note how many pull through the season well.

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Two groups of candidates are recognized for qualification by the board: (a) the Founders' Group; those who have already amply demonstrated their fitness as trained specialists in surgery; (b) those who having the general and special requirements needed successfully pass the qualifying examination. The examinations are both written and oral. The fee for the Founders' Group is \$25.00, and for Group b it is \$75.00. Re-examinations call for the same fee. After qualification there is no further financial obligation to the Board.

The Secretary is Dr. J. Stewart Rodman, 225 South Fifteenth St., Philadelphia, Pa.

The Tenth Annual Graduate Fortnight of the New York Academy of Medicine will be held at the Academy, 2 East 103rd St., New York City, from November 1 to 12, 1937. The program will be concerned with medical and surgical disorders of the urinary tract. The registration fee is \$3.00. The Secretary is Dr. Mahlon Ashford.

General

The International Congress of Anæsthetists will be held at the Congress Hotel, Chicago, from October 25th to 28th, during the Clinical Congress of Surgery. Further information can be obtained from the general secretary, Dr. F. H. McMechan, 318 Hotel Westlake, Rocky River, Ohio.

The Second Annual Congress of the American Urological Association is to be held at Buenos Aires, Argentina, from December 28th to January 4th. The first Congress was held at Rio de Janeiro in 1935. The following subjects will be discussed: genito-urinary hydatidosis; genital tuberculosis; the urography of excretion and endoscopic surgery of adenoma of the prostate. All necessary information can be obtained from the president of the Congress—Prof. Dr. Bernardino Maraini, Santa Fé, Buenos Aires, Argentina.

Book Reviews

The Development of Cardiac Enlargement. A Radiological Study. J. H. Palmer, M.D. (McGill), M.R.C.P. (Lond.). Medical Research Council, Special Report Series, No. 222. 49 pp., illustrated, 1s. His Majesty's Stationery Office, London, 1937.

In this valuable little monograph a suggestive and stimulating contribution has been made to our knowledge of the rate at which progressive enlargement or regression in size of the heart may take place in various chronic cardiac conditions, and the diagnostic and prognostic significance of such changes when they have occurred. Exact data for the establishment of such conclusions are not easy to obtain, for these must be based upon reliable records made upon the same patient at successive time intervals, and before positive generalizations can be drawn many such observations upon a number of different individuals presenting similar conditions must have been accumulated. Moreover, percussion and palpation of the apex beat, methods that are of positive value for the determination of gross cardiac enlargement, are not sufficiently exact in small alterations in area to provide adequate criteria for the estimation of progressive changes in heart-size. Radiology, on the other hand, the application of which to this problem is still in its infancy, does supply an objective method under which the personal equation may to a certain extent be eliminated and positive information obtained.

The present study was carried out by Dr. Palmer at the Cardiac Department of the London Hospital, at the suggestion of Dr. John Parkinson, with the

above considerations in view, and is based upon a large series of teleradiograms made on some 200 patients with chronic cardiac lesions culled chiefly from Dr. Parkinson's own service, either in that Hospital or his consultant practice, and collected by him over a period of many years with great foresight for the purpose of the present research. To this end a standardized technique had been followed throughout, 6 foot films being taken in full inspiration with 0.2 to 0.4 seconds' exposure. Orthodiographs were used in only a few cases. Interpretations were made by Dr. Palmer from the direct superposition of outlines traced by him on transparent paper from teleradiograms taken mostly in the antero-posterior diameter and at successive intervals in the same patient. Radiograms taken in one or other oblique diameter had unfortunately to be rejected in most cases as no satisfactory method had been found for placing the patient at the same angle to the film on different occasions for the purpose of exact comparisons. Changes in the height of the diaphragm were carefully taken into account. Alterations in the size of the heart or of its individual chambers are shown by the author as a broken line against the solid black contour of the original observation in graphic tracings. A large number of superimposed outlines are reproduced as cuts in this monograph, which thus presents a sort of miniature atlas with illuminating results. Among other points it was noted that in long-standing cases of failure some permanent increase in heart-size results, but failure of short duration, such as occurs in paroxysmal tachycardia, always passes off without leaving any sign; that in essential hypertension where progressive cardiac enlargement continues to develop after the blood pressure has become stabilized the presence of some additional factor, probably coronary sclerosis, may be assumed; also, that where no obvious cause can be found for a progressive cardiac enlargement in a person over 40 coronary disease must always be considered.

Dr. Palmer's communication is necessarily limited in scope to the cases on which it is based. As stated at the outset however, the data elicited are valuable so far as they go, the treatment is suggestive and the grouping into types is helpful, while the superimposed tracings establish a graphic method which should be extremely useful in the prosecution of further investigations upon selected cases. The up-to-date bibliography appended is confined to contributions in the literature upon the application of radiology to the problems of progressive cardiac enlargement.

Heart Disease. P. D. White, M.D. Second edition, 744 pp., illustrated, \$7.50. Macmillan, Toronto, 1937.

The first edition of this well and favourably known work appeared in 1931. Its general plan has been retained in this, the second edition, which has been thoroughly revised and brought up to date. This plan is logical and practical. The first part deals with the examination of the patient and the analysis of his signs and symptoms; part two, with the etiological types and causes of heart disease; part three, with the structural changes that develop in the heart and great vessels; part four, with disorders of function. The present volume has been reduced in size by the abridgement of Part I, the general principles and importance of the various methods of examination being still emphasized, but for details the reader must turn to other special works. Also, the bibliography has been reduced, only the most important key references being retained, with the addition of the titles of a few selected publications that have appeared during the last five years. The result is a volume of convenient proportions, well adapted to the needs of the medical student or the general practitioner. The author is an eminent consultant in the field of heart disease, and his book bears witness to his great experi-

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Perfringens Antitoxin	Tetanus Toxoid
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The first section deals with sterility, a problem of growing importance not only in general but special practice. The section dealing with the complications of pregnancy is of real interest, particularly as it presents the growing conservatism in connection with heart disease in pregnancy, the more recent views on endocrinopathy, the problem of acute surgical disease. The toxæmias of pregnancy come under this heading also and here the text is excellent.

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